



March 2, 2015

The Honorable Fred Upton, Chairman  
U.S. House of Representatives  
Committee on Energy and Commerce  
2125 Rayburn House Office Building  
Washington, D.C. 20515

Dear Chairman Upton:

AARP appreciates your efforts on the 21st Century Cures Initiative. AARP has taken a strong interest in this Initiative and we look forward to engaging in discussion with you and your staff as you continue to examine how the U.S. can promote greater innovation in the drug and medical device markets while also maintaining high standards of safety and effectiveness.

As noted in our previous comments in response to the Initiative's "Call to Action", medical innovation is important to AARP and all older Americans, who tend to use more prescription drugs and medical devices than any other segment of the population. However, AARP strongly believes that incentives for innovation must be appropriately balanced with ensuring that new treatments are safe and effective. Another equally important consideration is access: medical advances are meaningless if no one can afford to use them. We urge you to make these your guiding principles as you continue to develop the 21<sup>st</sup> Century Cures legislation.

AARP is a nonprofit, nonpartisan organization, with a membership of nearly 38 million that helps people turn their goals and dreams into real possibilities, strengthens communities, and fights for the issues that matter most to families. We appreciate that the discussion draft released on January 27 is intended to spur feedback on areas for improvement as you seek to develop a consensus driven package of proposals that can move forward on a bipartisan basis. With this in mind, we welcome the opportunity to share our comments. AARP has carefully reviewed the nearly 400-pages and we would like to share the following general comments as well as more specific comments on some of the individual proposals.

### **General Comments**

1. *The draft falls short of the goal of appropriately balancing new incentives with ensuring that consumers have access to affordable prescription drugs.*
2. *The draft would provide additional exclusivity periods to drug companies that are unnecessary and ineffective in terms of their ability to promote innovation, and they would almost certainly lead to increased costs for consumers.*

3. *The draft includes proposals that would weaken current drug and medical device safety and effectiveness standards, creating serious safety concerns.*
4. *The draft includes a number of proposals that seek to legislate decisions more appropriately left to experts at the Food and Drug Administration (FDA). Including such language would also effectively freeze science in place, defeating the stated intent of the legislation.*
5. *The draft does not address the overall lack of adequate resources for the FDA and National Institute Health (NIH), and individual proposals in the draft call for new responsibilities or activities without providing additional funding.*

As you look to enhance access to new and innovative treatments, AARP urges you to consider how the high cost of prescription drugs limits the availability of life-saving medications to those who are most in need of them. The recent increase in the number of specialty drugs with remarkably high prices and correspondingly high out-of-pocket costs in particular has spurred debate about whether the costs associated with these products are sustainable. While the committee should look at appropriate ways to promote greater innovation, it must also take a serious look at policies that are driving the high cost of prescription drugs.

**We believe that proposals to expand market exclusivity should only be used in extremely limited circumstances and only to reward drug companies for innovations that substantially improve upon existing therapies.** The proposals in the draft do not meet this threshold. There is also no evidence that increasing market exclusivity would result in an increase in innovation. In fact, there are indications that current incentives may instead favor market potential and profit. Consequently, any efforts to build on these existing incentives should be undertaken with an overabundance of caution to ensure that they have the intended effect.

### **Promising Proposals**

*Section 1001* would establish a framework building off of the Patient Focused Drug Development program at FDA for the meaningful collection of patient experience data in the regulatory process. This proposal could be useful if properly implemented, which includes appropriately managing risks and benefits and ensuring that drug manufacturers are not able to exert undue influence on FDA decision-making.

*Section 1201* would provide the NCATS with more flexibility on the use and funding of Other Transaction Authority (OTA) and *Section 1202* would authorize additional funds for NCATS' project to research the repurposing drugs for new uses. While there is value in funding these types of projects, AARP notes that any financial rewards from this government-funded research will flow to drug makers that may have declined to make similar research investments.

*Section 2001* would establish a public-private partnership based on the European Union (EU)'s Innovative Medicines Initiative to accelerate the discovery, development, and delivery in the United States of innovative cures, treatments, and preventive measures for

patients. It would be led by a board composed of government leaders from NIH, FDA, and CMS and leaders from medical device companies, drug companies, academic research institutions, patient groups, health plans, and others. While this consortium could play a valuable role, we have concerns that it is much broader in scope than the EU's Initiative, which has a dedicated budget of \$3.3 billion (in euros) for the next 10 years. This consortium will require dedicated funding if it is going to achieve its intended goals, including financial support from the drug and medical device industries.

*Sections 2061-2063* based on the SOFTWARE Act would help provide regulatory certainty for those developing apps and health information technologies. AARP is supportive of codifying what constitutes medical software—although it believes that FDA should be left to make that determination—and providing FDA with the authority to promulgate regulations to establish standards, policies, and procedures for these products, which have the potential to enhance the health care delivery experience for consumers by it making it more person-centered. However, we do have concerns that the language in this proposal is overly broad and would exclude some products that should be regulated. We also note that FDA's recent guidance provides greater clarity on its plans for regulating these products.

*Sections 2081, 2082, 2085, 2086, 2087, 2088, 2091, and 2092* would establish a data sharing framework to enable: 1) patients and physicians to better identify ongoing clinical trials, thereby increasing opportunities for patients in need of a treatment; 2) researchers and developers to use Medicare data for the purposes of improving the quality of patient care; and 3) a process for Congress to address issues identified by the President's Council of Advisors on Science and Technology. AARP sees these provisions as potentially adding value for both consumers and researchers. In particular, we believe developing a clinical trial registry system that provides information in a user friendly manner that is easily accessible and searchable would be a benefit to consumers. However, we have serious concerns about the use of Medicare data for “non-public” analyses and allowing these analyses to be sold. It is absolutely critical that all provisions under this proposal include enforceable privacy protections to guard against the release of individually identifiable information and the use of any related data for marketing.

*Section 2181* includes placeholder language for a national interoperable health information infrastructure proposal. AARP supports this goal and looks forward to seeing the details of this proposal.

*Section 2201* would require those receiving NIH grants to share their data, subject to confidentiality and trade secret protections. AARP supports providing the NIH director with the ability to require the public release of data generated from research grants. We urge the committee to also focus on ways to increase the transparency of drug companies' actual product development costs if they utilize taxpayer-funded research.

*Section 2241* would require the Secretary of Health and Human Services (HHS) to develop a plan to carry out a longitudinal study designed to improve the outcomes of patients with chronic disease. AARP supports this effort to improve the outcomes of patients with a chronic disease through better understanding of risk, transition from wellness to disease, disease progression, diagnosis, and other factors related to chronic disease, including

identifying potential areas for preventive or therapeutic intervention. However, given the substantial costs associated with longitudinal research, we strongly urge the committee to provide dedicated resources to support this effort.

*Section 2281* would require NIH to support projects that pursue innovative approaches to major challenges in biomedical research that are high-risk, but have the potential to lead to breakthroughs. While AARP supports the general idea behind this effort, we have strong concerns about its funding source. NIH funding is already limited and any redirected funds could instead be used to support less risky but equally beneficial research. We urge the committee to provide dedicated resources to support this effort.

*Section 2301* includes placeholder language for a precision medicine proposal. AARP supports this goal as broadly outlined in the President's Precision Medicine Initiative and we look forward to seeing the details of this proposal.

*Section 4008* AARP supports the goal of carrying out brain research at the NIH through the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative to assist researchers seeking new ways to treat, cure, and prevent brain disorders such as Alzheimer's and Parkinson's disease. We again urge the committee to authorize dedicated resources to continue this important work.

*Section 4181* would advance opportunities for telemedicine and new technologies to improve the delivery of quality health care services to Medicare beneficiaries. AARP is supportive of efforts to explore telemedicine and ways it can improve health access for underserved populations, such as individuals who live in rural communities.

*Section 4221* would allow seniors to better identify the out-of-pocket costs under Medicare for different treatments or services. AARP supports the goal of making out-of-pocket costs more transparent to beneficiaries when they are considering different treatment options in consultation with their physician. We urge the committee to ensure this proposal is adequately funded and that the information provided is reliable, regularly updated, and easily accessible.

*Sections 4281-4284* would help prevent high-risk Medicare beneficiaries from abusing controlled substances. AARP is generally supportive of efforts to address the problem of prescription drug fraud and abuse in the Medicare Part D program. We have supported proposals to ensure that the Medicare program does not pay for fraudulent prescriptions and diverted medications. In particular, we have supported provisions under the Protecting the Integrity of Medicare Act (PIMA) permitting Part D plan sponsors to establish "lock-in" programs for beneficiaries identified as high risk, and requiring them to use specific doctors and pharmacies for certain medications. We urge the committee to take the lock-in provisions of the PIMA legislation into consideration as it finalizes its proposal.

We strongly believe any program to address prescription drug fraud and abuse in Part D must focus not only on enrollees, but also on prescribers and pharmacies that often contribute to fraud and abuse problems. We urge the committee to ensure any lock-in program includes: 1) consultation with medical professionals to develop clinical evidence-

based criteria for identifying high risk enrollees; 2) protections to ensure appropriate beneficiary access to medically necessary drugs; 3) a clear process by which a person can appeal their plan's determination that they are a high risk individual; and (4) services to connect enrollees with behavioral health services, case management and other community resources. The program must also ensure that enrollee preferences for a specific prescriber or pharmacy are given special consideration when selections are made to ensure reasonable access.

We also appreciate that *Section 4283* includes recommendations from the HHS Office of the Inspector General to improve Part D oversight and monitoring, such as enhancing the activities of the Medicare Drug Integrity Contractor (MEDIC) and improving data sharing. We do have concerns the requirement for e-prescribing under *Section 4284* would present a burden for prescribers and pharmacies that do not have the necessary e-prescribing systems in place.

### **Proposals of Concern**

*Sections 1021-1024* would establish a process for FDA's consideration, and possible qualification, of surrogate endpoints and also allow FDA to use private-public partnerships to qualify other types of biomarkers. We are concerned that this provision seeks to legislate in an area of science more appropriately left to FDA. Further, legislating in this area could stall future advancements by restricting the agency to a process fixed in law. It should also be noted that the FDA is now seeking information to facilitate the development and qualification of biomarkers including opportunities for collaborative efforts that could lead to greater clarity on areas for improvement in the biomarker qualification process.

*Section 1041* would allow the FDA to approve a drug through the breakthrough therapy designation "when early stage clinical data provides sufficient evidence under the current safety and efficacy standards, considering the risks and benefits of the drug and the risks associated with the disease or condition for which unmet medical needs exist." This proposal raises serious safety concerns, as it is extremely unlikely that adverse events will be properly identified at this stage of the approval process.

*Sections 1061-1062* While AARP is generally supportive of efforts to spur the development of new antibiotic drugs, we do not support the new transferable exclusivity or "wild card exclusivity" program under *Section 1063*. We believe that this new form of exclusivity is unnecessary and would provide drug companies with the opportunity, for a minimal investment, to extend the monopoly period for any high cost drug in their portfolio—including blockbusters—at the great expense of consumers. We also believe this proposal is premature following enactment of the GAIN Act in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA), which was intended to incentivize the development of antibiotics by providing expedited approval and five years of additional exclusivity for antibiotics.

*Section 1064* would alter Medicare hospital payments with the intent of encouraging the development and use of new antimicrobial drugs for unmet medical needs. This provision would incentivize prescribers to utilize expensive new antimicrobials, which would increase Medicare spending. Further, while increased sales and utilization would likely encourage

the development of new antimicrobials, it could also lead to antimicrobial resistance if they are overused and/or not prescribed appropriately, diminishing their effectiveness.

*Sections 1081-1082* would establish a process at FDA for the designation and expedited review of devices that represent breakthrough technologies with the potential to address unmet medical needs. If FDA designates a medical device under this process and approves it under *Section 1161*, *Section 1162* would provide that the device would receive Medicare and Medicaid transitional coverage benefits. Based on our review of the current process for approving medical devices, there is no evidence this expedited review process is needed. We also have questions about how it would be determined that a device demonstrates “significant advantages” over existing approved or cleared alternatives. Overall, we believe that the bill language is far too broad for a breakthrough device designation.

*Section 1101* would establish an accelerated approval pathway for medical devices, similar to the pathway that currently exists for drugs. There is no evidence to support the need for an accelerated approval pathway for medical devices. We also have serious concerns about the use of a “reasonably likely” standard to predict clinical benefit of medical devices.

*Section 1161* is intended to provide more certainty regarding the regulations of communications on social media by FDA. AARP is concerned that this proposal is overly prescriptive and could lead to the publication of medical product information on social media without the necessary safety and effectiveness information. AARP also questions why this proposal is necessary given FDA’s recent and ongoing efforts to develop guidance for manufacturers who wish to use social media.

*Section 1181* would streamline the review process for adding indications to a drug label by allowing FDA to accept and review data summaries rather than full data packages. We are concerned this provision seeks to legislate in an area of science more appropriately left to FDA. It is critical that FDA continue to require a rigorous standard of data when considering new drug indications, particularly in light of the large and growing number of indications for many biologic medicines.<sup>1</sup>

*Sections 1221-1223* based on the MODDERN Cures Act would provide 15 years of exclusivity for drugs that treat patients with unmet medical needs, granting drug companies an unprecedented increase in exclusivity. AARP strongly opposes this proposal. The proposal is unnecessary to incentivize the development of new treatments and would be detrimental to consumers and other payers. Further, the language is far too broad: virtually any new drug with a new active ingredient, including those with only marginal improvements over existing therapies already on the market, would qualify for the additional exclusivity. Moreover, the proposal does not include any safeguards against product “evergreening,” which could extend the exclusivity beyond the 15 years that are provided, further delaying consumers’ access to lower cost alternatives.

---

<sup>1</sup> S.B. Dillon, “New Mechanisms and Expanded Indications for Biologic Therapies: A Perspective on Immunology Research and Development,” *Drug Discovery World*, Fall 2010.

*Section 1241* would extend exclusivity for two years for “significant improvements to existing molecules” under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FFDCA). These improvements could include developing new delivery systems, new drug combinations, and new formulations that lead to less adverse events and increase patient benefits and adherence. AARP strongly opposes this proposal. This proposal is unnecessary and would not lead to new innovation. The types of changes covered by this broadly constructed proposal are already made by drug companies when they engage in product “evergreening.” Drug companies should not be rewarded with two years of additional exclusivity for small changes that provide little or no improvement in therapeutic value above existing products.

*Section 1261* would provide six months of additional market exclusivity for a drug if the company establishes that the drug treats a rare disease and receives a rare disease indication from the FDA on its label. AARP strongly opposes this proposal. It is unnecessary to incentivize innovation for rare diseases, as evidenced by the record number of orphan drugs that were approved in 2014, as well as expectations that these trends will continue for the foreseeable future.<sup>2</sup>

*Section 2021* would create the Medical Product Innovation Advisory Commission. This Commission, which according to supportive materials is based on MedPAC, would advise Congress on issues related to the discovery, development, and delivery of new medical products. It is unclear why another advisory body is needed. FDA already uses 50 advisory committees and panels to obtain independent, expert advice on scientific, technical, and policy matters. AARP is concerned this advisory body could introduce serious conflict of interest concerns if individuals affiliated with for profit entities gain greater influence over drug and medical device policy-making.

*Section 2101* would authorize FDA to utilize “real world evidence,” or data about the usage, benefits, or risks of a drug derived from sources other than randomized clinical trials, including from observational studies and registries, and requires FDA to issue guidance on collecting such evidence. We are concerned that this proposal could lead drug companies to increase their efforts to encourage off-label prescribing with the goal of gaining new indications. These practices compromise patient safety and have already resulted in billions of dollars in civil and criminal fines.<sup>3</sup> Drug manufacturers that wish to profit from the increased utilization of their products should be willing to finance clinical studies of off-label uses.

*Section 2121* would allow for coverage with evidence development for new medical devices for Medicare beneficiaries participating in clinical trials. This proposal raises a number of safety concerns due to the range of devices where this policy would be applied, including implantable devices. AARP recommends a more cautious approach where CMS would: 1) publicly disclose and seek input regarding any plans for changing the Medicare coverage determination process and criteria for new technologies based on evidence using clinical trial and patient registry data; 2) allow independent researchers to review the

---

<sup>2</sup> E. Silverman, “There Are More Orphan Drugs and FDA Approvals Than Ever Before,” *Wall Street Journal*, February 17, 2015.

<sup>3</sup> M. Bobelian, “J&J’s \$2.2 Billion Settlement Won’t Stop Big Pharma’s Addiction to Off-Label Sales,” *Forbes*, November 12, 2013.

validity of data and methods that form the basis for Medicare coverage and publish the results of their findings; and 3) ensure that Medicare beneficiaries are not coerced to participate in Medicare trials or data registries and that they receive appropriate patient protections, including informed consent and privacy safeguards.

*Section 3031* would allow the FDA and sponsors to periodically evaluate whether post-approval studies remain scientifically warranted. AARP believes that post-approval studies are a critical component to ensuring medical products are not harmful to consumers, as many adverse effects are not detected until after the product is used in the broader population.<sup>4</sup> We also believe that allowing a review to be initiated “at the request of a responsible person” is far too vague and raises questions as to who would qualify to request a review. Further, this process would clearly be resource-intensive and there are no apparent limits on how many times or how often it could be requested.

*Section 4009* would remove the NIH’s National Center for Advancing Translational Science (NCATS) phase IIB clinical trial funding restriction. AARP is concerned this proposal would expand NIH’s funding support to include clinical trial activities at a phase of development that is more appropriate for industry funding.

*Section 4141* would make changes to the coverage requirements under the Medicare program for certain disposable medical technologies. AARP believes that competitive bidding should be used for pricing all durable medical equipment as long as quality and access are not compromised by the competitive bidding process. Further, there is no evidence that a new category of disposable medical technology is needed.

*Section 4161* would make changes to the Medicare local coverage determination (LCD) process. AARP is generally concerned that the changes outlined under this proposal would provide companies with additional opportunities to influence LCDs by effectively allowing them to lobby Medicare administrative contractors (MACs). It would also make it considerably more burdensome for MACs to appropriately deny coverage.

*Section 4301* would establish a program that allows for patients to access medical device treatments sooner than otherwise would be available. AARP is concerned this proposal could create serious safety issues as manufacturers would be allowed to offer their products without FDA approval indefinitely. It would also place an additional burden on providers, who would be forced to track which devices are included in the program in order to initiate the processes required for payment.

*Section 4401* would clarify the law regarding Research Use Only (RUO) labeled products. AARP is concerned that this proposal raises safety issues because it would allow manufacturers to promote off label use for products with research use only labeling.

*Section 5001* would extend the exclusivity period granted to a first-to-file generic and biosimilar manufacturer if the product in question is designated as an American-manufactured drug. AARP opposes this proposal, which is unnecessary and would reduce competition by delaying the introduction of less expensive generic drugs and follow-on biologics.

---

<sup>4</sup> IOM, *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*, 2012.



*Section 5061* would allow FDA to rely on third party accredited bodies to certify minor manufacturing changes. AARP urges the committee to act in an overabundance of caution when considering any changes that would decentralize the approval of manufacturing changes. We believe it is critical that FDA be able to maintain its role in reviewing all product changes, even the most minor of which can have serious health and safety implications.

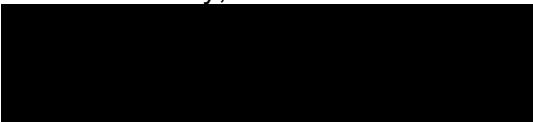
*Section 5062* would clarify that valid scientific evidence includes “well-documented, real world evidence” gathered from clinical registries and studies published in peer-reviewed journals. AARP is concerned this proposal would lead drug manufacturers to increase their efforts to encourage off-label prescribing. This proposal would also enable companies to bypass the clinical trials process, potentially compromising patient safety. Drug manufacturers that wish to profit from the increased utilization of their products should be willing to finance clinical studies of off-label uses.

*Section 5064* would change the process of government recognition of standards set by the medical community. AARP is concerned that this proposal inappropriately seeks to force FDA to follow standards set by the medical community that may not be evidence-based (e.g., off-label prescribing) and would be an ineffective use of limited FDA resources.

*Section 5068* would streamline the FDA committee advisory process. AARP is concerned this proposal seeks to make changes to advisory committee processes that are more appropriately left to the agency to determine in consultation with stakeholders under its administrative authority. It also introduces conflict of interest concerns by allowing individuals affiliated with for profit entities to gain greater influence over drug and medical device policy-making.

In closing, we must stress the importance of balance and urge the committee to take a careful, measured approach that can gain the support of both industry and consumer advocacy groups. While we strongly support promoting the development of innovative treatments and cures, we believe it is critically important that these treatments are safe, effective and affordable to consumers. Thank you for the opportunity to comment on these important issues. If you have any questions, please do not hesitate to contact me or Ariel Gonzalez on our Government Affairs staff at [agonzalez@aarp.org](mailto:agonzalez@aarp.org) or KJ Hertz at [khertz@aarp.org](mailto:khertz@aarp.org) or 202-434-3770.

Sincerely,

A large black rectangular redaction box covering the signature area.

Joyce A. Rogers  
Senior Vice President, Government Affairs, AARP

cc: The Honorable Frank Pallone, All Energy and Commerce Committee Members



Chairman of the Board  
Bernard P. Dennis

President  
Elliott M. Antman, MD, FAHA

Chairman-elect  
Alvin L. Royse, JD, CPA

President-elect  
Mark A. Creager, MD, FAHA

Immediate Past  
Chairman of the Board  
Ron W. Haddock

Immediate Past President  
Mariell Jessup, MD, FAHA

Treasurer  
David A. Bush

Directors  
Mary Ann Bauman, MD  
Mary Cushman, MD, MSc, FAHA  
Mitchell S. V. Elkind, MD, MS, FAHA  
Robert A. Harrington, MD  
Steven R. Houser, PhD, FAHA  
Marsha Jones  
Willie E. Lawrence, Jr., MD, FAHA  
Pegui Mariduena, CMC, MBA  
John J. Mullenholz  
Bertram L. Scott  
David A. Spina  
Bernard J. Tyson  
Raymond P. Vara, Jr.  
John J. Warner, MD  
Alexander P. Almazan, PA - Liaison  
James J. Postl - Liaison

Chief Executive Officer  
Nancy A. Brown

Chief Mission Officer  
Meighan Girgus

Chief Diversity Officer  
Gerald Johnson, II

Chief Administrative Officer &  
Chief Financial Officer  
Sunder D. Joshi

Chief Science & Medical Officer  
Rose Marie Robertson, MD, FAHA

Chief Development Officer  
Suzie Upton

Chief of Staff to the CEO  
Laura Sol

Deputy Chief Medical Officer  
Eduardo Sanchez, MD, MPH

Executive Vice President,  
Corporate Secretary &  
General Counsel  
Lynne M. Darrouzet, Esq.

Advocacy Department  
1150 Connecticut Ave., NW | Suite 300 | Washington, DC 20036  
P 202-785-7900 | F 202-785-7950 | [www.heart.org](http://www.heart.org)

March 13, 2015

Committee on Energy and Commerce  
2125 Rayburn House Office Building  
Washington, DC 20515

## Re: 21<sup>st</sup> Century Cures Discussion Document

Dear Chairman Upton and Representative DeGette:

On behalf of the American Heart Association (AHA), including the American Stroke Association (ASA) and over 22.5 million volunteers and supporters across the country, we appreciate the opportunity to provide comments regarding the 21<sup>st</sup> Century Cures Act discussion draft. We applaud your work and the significant attention the Committee on Energy and Commerce has given this initiative over the past year. In addition, we appreciate your continued commitment to engaging stakeholders to find ways to improve patient care and access to treatments. We are grateful for the numerous opportunities your Committee has provided the AHA/ASA and other stakeholders to inform this initiative, including allowing the AHA/ASA to provide testimony at the Subcommittee's laboratory developed test hearing on September 9, 2014.

We also commend the Committee for releasing its discussion draft and hope that you will continue to provide additional opportunities for stakeholders to share thoughts as the bill works its way through the legislative process.

While we share your overall goals of advancing biomedical research, engaging patients in the drug discovery and development process, and increasing access to critical drug therapies and products, it is crucial that any legislative proposal maintain necessary patient safety protections and ensures the efficacy of all medical products. Furthermore, it is important to recognize that the Food and Drug Administration (FDA) has made considerable progress in recent years in expeditiously bringing new, innovative products to market that improve quality of care for patients. In 2014, the FDA approved the highest number of novel new drugs since 1996, including 17 new therapies to treat rare diseases. The FDA's

*"Building healthier lives, free of  
cardiovascular diseases and stroke."*

life is why™ es por la vida™ 全为生命™

existing regulatory authorities allowed it to evaluate and bring these new drugs to market while maintaining its rigorous safety standards. We strongly believe that these safety and efficacy safeguards must remain in place.

To that end, we have highlighted a number of provisions in the discussion draft that we believe, as currently written, do not strike the appropriate balance between reducing a patient's risk from harm while facilitating the discovery of better treatments and cures for cardiovascular diseases (CVD). These provisions primarily would change or accelerate processes within the FDA drug and device approval process, as well as allow new evidentiary standards to be submitted for review. We believe these provisions may have the potential to yield unsafe products for patients or expand access to products that may be prematurely determined to be safe and effective. We also must ensure that efforts to speed approval do not inadvertently undermine the recruitment of patients, particularly patients with diverse backgrounds, to later phase trials. In addition, we have also noted a number of proposed provisions that would make reforms at the National Institutes of Health (NIH) that we believe may have negative consequences on the agency and federally funded research initiatives.

There are, however, a number of provisions included below that we support and would encourage the Committee to include in future legislative drafts. In some cases, we have offered suggestions for ways they could be made even more beneficial for patients. We have also included suggestions for two provisions that are not currently in the bill. These include language in the bill that would expand the use of telestroke care – or the use of telemedicine in the treatment of stroke – by allowing Medicare to reimburse for telehealth services that originate in urban and suburban areas, as well as in rural areas, and a provision that would create new incentives for the development of high impact preventative medicines.

Overall, we applaud the Committee for exploring ways to expand opportunities for patients to provide input during the drug and biologic review process, create new public-private partnerships that would work together to bring new cures and treatments to patients, facilitate data sharing, and reduce economic burdens for patients to access the care they need. While we know there are many diseases without any treatment options or cures, we hope the Committee continues to recognize improving patient health outcomes in the United States depends not only on accelerating innovation in the drug and device discovery and development process but also requires that existing therapies for which there is well-established science and recommended use in authoritative guidelines are applied to the full effect for the benefit of individuals and population health. Therefore, we encourage the Committee to also consider the need for innovation in the dissemination and scaling up of existing interventions.

We recognize these are challenging issues, which is why we also remain committed to advancing promising approaches in the regulatory process that bring together all stakeholder perspectives to appropriately address the balance between comprehensive knowledge on the benefits and risks of therapies while providing timely patient access. For instance, the AHA/ASA considers the concept of adaptive licensing as one potential approach to aligning a patient's need for access to new treatments with the desire to spur innovation and to maintain rigorous safety oversight. In short, an adaptive licensing approach would provide regulatory flexibility by allowing provisional approval of a product when combined with ongoing evaluation, surveillance, and

evidence gathering prior to granting full approval. Such an approach, especially when coupled with ongoing communication between patients and practitioners that acknowledges the evolving uncertainties of products and their use as additional knowledge is gathered, may be an additional concept for the Committee to explore as it seeks to address current challenges in the drug and device approval process.

We hope that the Committee carefully considers the following comments as it works to advance this legislation.

### Title I – Putting Patients First By Incorporating Their Perspectives into the Regulatory Process and Addressing Unmet Needs

#### *Section 1001*

We support the need to expand opportunities for patients to provide input during the drug and biologic review process. Patients can provide a unique perspective on the impact of a disease, the severity of the condition, and the adequacy of the existing treatment options. Patients can also provide valuable information on the benefits they would like a drug to deliver and the acceptable level of risk. There are currently a number of cardiovascular diseases, including atrial fibrillation, stroke, and peripheral arterial disease, that affect a significant portion of the U.S. population and affect functioning and activities of daily living yet lack drug therapies that sufficiently address treatment needs. We agree that there should be a framework for incorporating the patient experience into the regulatory decision-making process, and we would look forward to working with the FDA in creating and implementing the framework proposed in this legislation.

#### *Sections 1021-1024*

We appreciate the Committee's interest in developing and revising standards for determining qualified surrogate endpoints and finding new ways to approve therapies, as well as allowing the FDA to enter into partnerships to review requests for qualifying biomarkers for use other than as surrogate endpoints. We understand that this provision is reasonable for certain disorders and therapeutic strategies, and it could be potentially valuable when a surrogate marker appears to predict toxicity in a subset of a target population. We would like to strongly caution the Committee, however, that these provisions may also adversely affect the public health should a biomarker be falsely accepted as a surrogate endpoint without robust scientific evidence, particularly as there are many examples of flawed reliance on surrogates in the evolution of cardiovascular pharmacologic therapies. For instance, there have previously been biomarkers that represented plausible surrogate endpoints – such as reduced rate of ventricular premature beats following a heart attack or cardiac output in congestive heart failure – that failed to predict the expected clinical benefit when tested in outcome trials. As a result, using biomarkers as surrogate endpoints which are later discovered to not improve health outcomes could allow for the approval of products that cause harm or death in certain patient populations.

#### *Sections 1041, 1081-1082, and 1101*

We recognize the Committee's intent to find ways to accelerate processes for bringing new breakthrough drugs and devices to market. We also believe that the FDA shares this desire, as it currently has existing pathways to achieve this goal while providing broad discretion and

flexibility in applying statutory standards for safety and efficacy. This includes the use of existing pathways for exceptional patient access to early stage investigational drugs for treatment use (21 CFR part 312, subpart I) and for drugs intended to treat life-threatening and severely-debilitating illnesses (21 CFR part 312, subpart E). As currently written, we believe that the provisions that rely on very early stage clinical safety and efficacy data are overly broad, subject to misinterpretation, and have the potential for major risk of patient harm or costs from unanticipated complications. The reliance on early data from shorter, smaller trials could potentially result in the approval of drugs or devices based on insufficient evidence regarding efficacy and, importantly, safety. This could ultimately be particularly detrimental for women, minorities and the elderly, who are frequently underrepresented in early phase trials even more than they are in phase 3 trials.

On the other hand, we believe provisions that would accelerate the approval of breakthrough devices could be potentially beneficial for a limited subset of medical devices. However, provisions in the discussion draft should be tailored so that accelerated approval would be used sparingly. The goal should be to target true breakthrough products and only those that are rigorously qualified for major unmet clinical needs or represent major innovations.

Moreover, we caution that, although Section 1082 is currently placeholder language, the Committee should not include language that would require Medicare and Medicaid to cover a device approved through the priority review for breakthrough device process because the device may not be appropriate for the Medicare population.

#### *Section 1181*

We caution the Committee that efforts to create a streamlined data review program for new indications could undermine efforts to ensure a sufficiently robust dataset to allow appropriate demographic subgroup analyses for safety and efficacy, particularly if the test for the initial indication was conducted in a relatively homogeneous population. Such subgroup analyses by sex, race and ethnicity, and age can help to lead to better-targeted therapies, the ultimate goal of precision medicine initiatives.

#### *Section 1241*

While we recognize the need to create incentives for industry to invest in new products that would lead to fewer adverse events and increase patient benefits and adherence, we are concerned that this provision could make drugs more expensive for patients by extending exclusivity. While such a provision might be beneficial for a limited subset of products, such as those to treat certain rare diseases and certain preventative medications, we believe strongly that patients should have access to affordable medications and caution that such a provision could delay access to generic, lower-cost drugs. We emphasize this point since multiple studies have shown the disturbing fact that many patients do not comply with a prescribed, evidence-based regimen because of cost.

However, we strongly encourage the Committee to include a narrowly crafted provision that would create a process to extend patent life for high impact preventive therapies to allow greater innovation by industry, improve chances of successfully decreasing burden of illness, and improve public health. The long duration of follow-up required for primary prevention trials

often erodes the patent life of a drug, leaving little financial incentive for companies to invest resources in this area. This is particularly an issue for stroke research and neurodegenerative diseases. Clinical trials to test the efficacy of preventive strategies for stroke would require early interventions and prolonged follow-up, perhaps decades, to show effects. The long duration of these clinical trials represent a substantial portion of a drug patent, making it prohibitive for companies to even consider developing drugs for prevention.

## Title II – Building the Foundation for 21<sup>st</sup> Century Medicine, Including Helping Young Scientists

### *Section 2001*

We applaud the Committee for including this provision. We strongly support collaboration across all stakeholders and sectors of the health care system to advance new cures and treatments for patients.

### *Sections 2061-2063*

We believe this is an important issue for the Committee to consider, due to the great potential for innovation for mobile technologies that could improve patient health. We also understand, however, that the FDA is currently addressing similar issues and how it would oversee these types of technologies. It is important when both the Committee and the FDA consider additional oversight or regulation of medical technologies they consider how this might increase regulatory hurdles, particularly for clinical decision support software, and how this would impact patient management.

### *Sections 2081-2092*

Expanding access and enhancing clinical trials transparency, as well as allowing qualified clinical data registries to access Medicare data, could have major potential for quality improvement and research purposes. For example, the AHA/ASA has developed a number of quality improvement programs that include clinical registries to aggregate patient care data and generate real-time reports for providers that assess their performance compared to national benchmarks. Access to timely Medicare data would enhance these quality improvement efforts, and we encourage the Committee to provide clarity as to the timeliness of the Medicare claims data that would be available, as well as clarify that if a registry is a “qualified clinical data registry” for the purposes of the Centers for Medicare and Medicaid Services (CMS) quality reporting programs then access to Medicare claims data should be provided at no cost to such entities or organizations. It is imperative that claims data be timely in their release. As noted above, registries can provide real-time information and if the lag for administrative data is too far behind the clinical data, access to that data would not provide any significant benefit. We also recommend that the Committee provide additional clarity about the need to develop and implement appropriate use criteria as part of the data-sharing framework and wish to emphasize that we look forward to working with the Committee on establishing the principles for responsible data-sharing.

#### *Section 2101*

We recognize that the intent is to expand access to data that may be useful in the FDA approval process beyond the current data standards, such as pragmatic “real world” randomized controlled trials embedded within registries and electronic health records to generate a high level evidence at lower cost. While the FDA should be encouraged to consider this type of data, this provision should not confound useful data with the “real world” observational data emphasized in this provision. Additionally, the Committee should clarify that the “real world evidence” described in this section, as currently written, should only be used for postmarket approval processes and not for primary approval of new therapies.

#### *Section 2121*

We support this provision and believe it is important for Medicare to cover the cost of medical devices that are for coverage with evidence development that a beneficiary receives in order to ease the economic burdens of accessing these treatments.

#### *Section 2161*

We have previously submitted more detailed comments on the regulation of diagnostic devices and laboratory developed tests (LDTs), as well as provided testimony on this issue during a September 9, 2014 Subcommittee hearing. To briefly reiterate our previous comments, we support the FDA’s recently released draft guidance documents and its proposed approach for regulating LDTs in a phased-in, risk-based manner. We believe this is the best approach for ensuring the appropriate level of oversight for LDTs in order to reassure patients and providers on the reliability and usefulness of these tests. We strongly encourage the Committee not to include language in any legislative proposal that impedes or prevents the FDA from acting swiftly to finalize its guidance and phasing-in regulation of these tests.

#### *Section 2181*

While this section is only a placeholder, we look forward to reviewing this provision and believe that it is important that health IT systems can adequately communicate with one another in order to improve patient care, particularly as patients with CVD and stroke frequently require multiple providers to manager their conditions.

#### *Section 2201*

We support this provision in principle and believe there are already policies in place to encourage data sharing, such as the NIH requiring certain applicants to address data sharing in their funding applications. We encourage the Committee to include additional clarity and information on this provision and how it would be implemented in order to ensure the appropriate governance of shared data – such as the timeframe when data would need to be made public – in order to allow the primary researchers the appropriate opportunity to publish their research.

#### *Section 2221*

We believe that expanding access to patient health information while providing sufficient protections could be a potentially powerful tool to address critical research needs. However, we ask that the Committee provide additional clarity as to what type of health care data these provisions would apply to, whether or not it includes health data collected as part of routine care,

how this would apply to specific episodes of care in addition to care taking place over a course of time in multiple health care settings, and how to make captured data meaningful to improve patient care.

#### *Section 2241*

We support this provision and recommend the Committee acknowledge and recommend using clinical registries as a mechanism for such a longitudinal study.

#### *Section 2301*

We support the Committee's interest in fostering precision medicine and look forward to reviewing language under this section in future legislative proposals. We strongly believe that precision medicine research will help arm us with a deeper understanding of the deadly diseases that affect so many Americans, including CVD. Like the Committee, the AHA/ASA is also committed to cutting-edge heart and stroke research in pursuit of personalized cures. That is one of the major reasons why we launched the Cardiovascular Genome Phenome Study (CVGPS) last year. CVGPS combines the power of long-term population studies with genomic analysis for a 360-degree look at heart health and disease. Precision medicine initiatives are essential for tapping research for hidden insights that will speed the discovery of better treatments to improve the cardiovascular health of our nation.

### Title III – Modernizing Clinical Trials

#### *Section 3002*

We support this provision and the concept of a central institutional review board to help minimize regulatory duplication and unnecessary delays in research.

#### *Section 3031*

We are concerned that allowing the FDA and sponsors to periodically evaluate whether post-approval studies remain scientifically warranted could potentially lead to fewer postmarket studies and give too much flexibility for manufacturers to renegotiate their postmarket study requirements.

#### *Section 3041 and 3061*

We support these provisions and encourage the Committee to increase resources to support pediatric research.

### Title IV – Accelerating the Discovery, Development, and Delivery Cycle and Continuing 21<sup>st</sup> Century Innovation at NIH, FDA, CDC, and CMS

#### *Sections 4001, 4003, 4004, and 4005*

While we support these provisions in principle and appreciate the Committee's interest in addressing accountability at the NIH and requiring planning to accelerate the discovery of new cures, we strongly caution the Committee not to duplicate efforts already underway at the NIH or place additional burdens on the NIH that would divert its ongoing research initiatives. For example, the FY2015 omnibus appropriations legislation included a similar provision to require the NIH to issue a strategic plan. As currently written, it is not clear how the strategic focus



areas will be determined, even though the language would ensure that certain diseases are given priority, and how these strategic areas will affect resource allocation decisions. We also cannot support provisions that require term limits of NIH institutes and center directors, and provisions that would require institute or national center directors to personally review and approve grants. We support language that may be included in Section 4003 that would better facilitate and ease travel restrictions for NIH researchers.

#### *Sections 4002, 4007, and 4008*

We support these provisions and the need to reduce administrative burdens on research. We also strongly support and encourage the Committee to include additional funding for NIH.

#### *Section 4021*

We support this provision and recommend that the language specifically include references to stroke. We understand that the text is currently drafted to ensure that a surveillance system be developed for all neurological diseases, and it would not be possible to mention all such diseases. However, we believe that it would be appropriate and helpful to mention stroke, particularly as it is the 5<sup>th</sup> leading cause of death, the leading cause of long-term disability, and the 2<sup>nd</sup> leading cause of dementia in the United States. We also recommend specifically mentioning rehabilitation as part of the information collected and stored in the surveillance system under subsection (c)(3)(D). In addition to information related to the incidence and prevalence of neurological diseases, we also recommend that the surveillance system collect data on recurrence rates for neurological diseases, as well as extend the scope to include major cardiovascular events and heart failure while providing sufficient funding to support this added scope of surveillance.

#### *Section 4161*

We support this concept and agree that reform is needed for the Medicare local coverage determination process, particularly as there is the need for consistency of local and national coverage determination processes and encourage the Committee to align the public comment period for national coverage determinations with this provision.

#### *Section 4181*

We have previously submitted more detailed comments about the Telehealth Subtitle to the Committee's telehealth working group and look forward to seeing a revised version of this section soon that will hopefully address these comments. To briefly reiterate our earlier comments, however, while we support the intent of this provision, we are concerned that it leaves too much discretion to CMS to develop a list of telehealth services covered under Medicare Part A and B when CMS has not yet acted within its current authority to support telehealth services. In addition, we believe that this provision would place certain requirements on CMS to certify services – such as ensuring that covered telehealth services would reduce Medicare spending, as opposed to federal health spending, or be budget neutral – that would make it difficult to expand these services.

We also strongly encourage the Committee to address the Medicare reimbursement barrier that would help make telestroke care more widely available by allowing Medicare to reimburse for telehealth services that originate in urban and suburban areas, as well as in rural areas.

Numerous studies have demonstrated that the use telestroke can be helpful in improving access to high quality stroke care. The use of telestroke has shown great promise in improving patient access to recommended stroke treatments in both rural and other “neurologically underserved” areas – enhancing access to high quality stroke consults and increasing the number of patients who receive tPA by six-fold in some hospitals. Moreover, the outcomes for stroke patients who are cared for in hospitals with telemedicine support have been comparable to those achieved in other stroke centers and have surpassed those achieved by general hospitals without telemedicine support or stroke units.

In addition to improving access to the recommended care, we believe the greater use of telestroke will also result in healthcare cost savings to the federal government by reducing disability and the need for more extensive medical care. Several studies have clearly shown that the use of tPA is cost-saving for stroke care, including a study published in the *New England Journal of Medicine* that showed patients receiving clot-busting therapy were at least 30 percent more likely to have minimal or no disability at three months when compared to patients who did not receive this treatment. The study also found that these patients have shorter hospital stays and are more frequently discharged to their homes rather than to more costly nursing homes. Another study found that the average cost savings when administering tPA was \$4,255.00 per treated patient, largely as a result of decreased need for nursing home care and decreased utilization of rehabilitation by the patient who received treatment. We have provided the Committee’s telehealth working group with legislative language for this provision and strongly urge that this be included in future drafts of the bill.

#### *Section 4362*

We support this provision and efforts to improve care for children with complex medical conditions, such as congenital heart defects.

#### *Section 4381*

We support this provision and the need to exclude continuing medical education from requirements under the Sunshine Act. We urge the Committee to include an additional exemption for indirect payments to voluntary health agencies (VHA) when the manufacturer gives complete discretion to the VHA to select the recipients of research funding.

### Title V – Modernizing Medical Product Regulation

#### *Section 5062*

As noted above, we have significant reservations about using certain “real world evidence” as the basis for determining effectiveness of drugs and devices. This provision is also particularly concerning as it would constrain the FDA from requiring the submission of data from studies published in peer-reviewed journals. One potential consequence could mean that the FDA may not be able to determine whether or not there was adequate representation of patient subgroups in such studies in order to ensure that products are safe and effective for all who might use them.

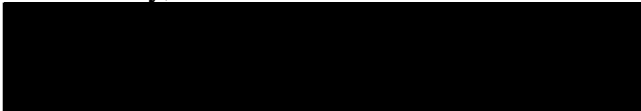
## Conclusion

We thank the Committee for providing the opportunity for the American Heart Association/American Stroke Association to provide feedback on the 21<sup>st</sup> Century Cures Act discussion draft. We applaud the Committee and staff for the significant amount of energy and attention it has given this initiative and agree with the Committee's intent to find new ways to discover, develop, and deliver new cures for patients. As you address these challenges, we strongly encourage the Committee to maintain processes that are necessary to maintain the rigorous review of the safety and efficacy of medical products before they are approved for use. It is critical that any legislation keep the appropriate balance between accelerating the drug and device discovery process and ensuring products are safe and effective for patients. We also encourage the Committee to recognize and explore ways to also facilitate innovation in disseminating information and the scaling up of existing interventions. Finally, it is critical that the Committee ensure the FDA, NIH, and other agencies have the resources they need should new requirements be placed on them.

While we noted several provisions that we support and are encouraged to see included in the draft legislation, we also believe there are a number of provisions identified above that do not appropriately balance patient safety needs with the desire to bring new drugs and devices quickly to market. We hope that these concerns will be addressed during the legislative process. If you have any questions or would like to discuss any of our comments and recommendations, please contact Kevin Kaiser at 202-785-7931 or via email at [kevin.kaiser@heart.org](mailto:kevin.kaiser@heart.org).

Again, thank you for your careful consideration of our comments, and we look forward to continuing to work with the Committee on these critical issues.

Sincerely,



Elliott M. Antman, MD, FAHA  
President  
American Heart Association



March 12, 2015

The Honorable Fred Upton  
Chairman  
Energy & Commerce Committee  
U.S. House of Representatives  
2125 Rayburn House Office Building  
Washington, D.C. 20515

The Honorable Diana DeGette  
Member  
Energy & Commerce Committee  
U.S. House of Representatives  
2368 Rayburn House Office Building  
Washington, D.C. 20515

**Re: Biocom's Comments in Response to the Energy & Commerce Committee's 21<sup>st</sup> Century Cures Discussion Draft**

Dear Chairman Upton and Congresswoman DeGette:

Biocom represents the Southern California life science industry, which includes biopharmaceutical, medical device, and diagnostic companies, universities and research institutions, as well as service providers and patient groups. With more than 660 members dedicated to developing life-enhancing and life-saving drugs, medical devices, and biologics for patients in need, Biocom leads advocacy efforts to positively influence the region's life science community in the development and delivery of innovative products.

Biocom commends you on releasing the 21<sup>st</sup> Century Cures discussion draft, which intends to accelerate the discovery and development of treatments and cures, and modernize the delivery of care. We applaud your leadership and the Energy & Commerce Committee's continued efforts to improve our nation's innovation ecosystem. The document offers a broad and targeted set of proposals that address some of the most pressing challenges that currently hinder biomedical innovation and the development of the next generation of modern medicines.

Please find below our feedback on specific provisions of high interest to our industry. We thank you for the opportunity to provide comments and look forward to continuing working with you as the proposal moves through the legislative process.

## Title I – Putting Patients First by Incorporating their Perspectives into the Regulatory Process and Addressing Unmet Needs

### **Subtitle B- Surrogate Endpoint Qualification and Utilization**

Biocom supports this provision which establishes clear standards for biomarker acceptance and qualification, thus providing drug sponsors with much needed certainty and transparency. The use of biomarkers during the drug development process has enabled clinicians to define subcategories of patients and identify risk groups, which has significantly increased treatment efficacy, predictability, and safety. Given the vital role of biomarkers in clinical development and medical practice, ***Biocom recommends that the Committee expands the provision to include standards and processes for the qualification of the full spectrum of biomarkers, such as pre-clinical and clinical biomarkers.***

### **Subtitle C – Approval of Breakthrough Therapies**

Biocom supports this provision.

### **Subtitle E – Priority Review for Breakthrough Devices**

Biocom strongly supports this provision and ***supports including legislative language to require the Centers for Medicare and Medicaid Services (CMS) to establish coverage benefits for medical devices and diagnostics approved under the breakthrough devices designation, in lieu of the placeholder (section 1082).***

### **Subtitle K – Cures Acceleration Network**

Biocom supports this provision. Additional comments under Title IV, Subtitle A.

### **Subtitle L – Dormant Therapies**

Biocom supports this concept and looks forward to continuing the dialogue as the Committee finalizes this provision's language.

### **Subtitle M – New Therapeutic Entities**

Biocom supports this provision.

## Title II – Building the Foundation for 21<sup>st</sup> Century Medicine Including Helping Young Scientists

### **Subtitle E – Sensible Oversight For Technology Which Advances Regulatory Efficiency (SOFTWARE)**

Biocom supports platform-agnostic regulations of digital health technologies and believes that products with medical intended uses should be regulated by the Food and Drug Administration (FDA), while those representing a lower risk for patients could benefit from a less stringent set of regulations.

FDA's recently released final guidance documents *Mobile Medical Applications* and *Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices* provided the industry with a clear regulatory framework and much needed predictability. In addition, the FDA released two draft guidance documents last month, *General Wellness: Policy for Low Risk Devices* and *Medical Device Accessories: Defining Accessories and Classification Pathway for New Accessory Types*, which clarify that FDA does not intend to take enforcement action in connection with low-risk general wellness products and establish a new risk-based approach to medical device accessories.

While Biocom does not oppose the Committee's intent to create a new "health software" category to provide greater regulatory certainty, we have concerns with the scope of the "medical software" category, which encompasses technologies currently regulated by the FDA as medical devices and that we believe should continue to be regulated as such.

***Biocom recommends removing the medical software provision, which we believe will create a duplicative and therefore confusing framework for the regulation of certain digital health technologies.*** We look forward to working with the Committee on this important issue.

### **Subtitle G – Utilizing Real-World Evidence**

Biocom strongly supports this provision.

### **Subtitle K - Interoperability**

The exchange of data through Electronic Health Records (EHRs) has led to the development of more coordinated health care systems and significantly improved the quality, efficiency, and safety of health care delivery. Nevertheless, incentives for the adoption of interoperable EHRs in CMS' EHR incentive payment program - popularly referred to as "Meaningful Use"- continue to lack references to remote patient monitoring technologies and patient generated health data (PGHD). To date, meaningful use has focused on Certified EHRs, EHR modules, and EHR systems, but has yet to fully encourage the involvement of patients and families in their care.

***Biocom supports legislative language directing CMS to ensure that future stages of meaningful use requirements allow the use and integration of PGHD into EHRs.*** Doing so would incentivize eligible providers to embrace the use of remote monitoring technologies, which would highly benefit patients, especially the most chronically ill, who can be monitored in their homes and outside of healthcare institutions.

In addition, the increased use of Electronic Health Records (EHRs) and other online platforms holds the potential to modernize not only the delivery of care but also the collection of clinical trial data. For example, instead of requiring clinical trial investigators to complete traditional case report forms, clinical trial data could be obtained directly from EHRs or other online platforms, which are routinely completed by treating physicians as part of patients' care. Mobile sensors and wearable devices can help monitor patients' physiological data and streamline the collection of information to be used by study investigators. This approach would enable the study to be conducted more efficiently, alongside the delivery of care.

However, because it is unclear if regulators will accept data generated using these methods, clinical trial sponsors have been reluctant to fully incorporate these technologies into registrational studies. ***Biocom recommends including legislative language that supports the development of standards for the use of EHRs and other online platforms in clinical research.***

#### **Subtitle O – Helping Young Emerging Scientists**

Biocom supports this provision. Additional comments under Title IV, Subtitle A.

#### **Subtitle P – Fostering High-Risk, High-Reward Science**

Biocom supports this provision. Additional comments under Title IV, Subtitle A.

#### **Subtitle Q – Precision Medicine**

Precision medicine has undergone tremendous growth these past decades and holds promise for revolutionizing the delivery of care as we know it, by selecting the most effective treatments for patients based on their individual characteristics. Advances in precision medicine have already led to breakthrough discoveries and treatments that are tailored to the genetic makeup of patients or genetic profile of a disease, but renewed efforts are necessary to further our understanding of the biology of diseases and integrate precision medicine into every day clinical practice.

The President's Precision Medicine Initiative will build on advances in genomics to accelerate biomedical research and the development of new treatments, and foster a new era of personalized medical care.

***Biocom recommends including the President's Precision Medicine Initiative in the 21<sup>st</sup> Century Cures Act, in lieu of current placeholder language, and authorizing additional funding for the National Institutes of Health (NIH) to cover the cost of the initiative.***

### Title III- Modernizing Clinical Trials

#### **Subtitle B – Broader Application of Bayesian Statistics and Adaptive Trial Designs**

Biocom strongly supports this provision.

#### **Subtitle C - Post-Approval Studies and Clinical Trials**

Biocom supports ensuring that a clearly defined process is in place to reassess the scientific validity and timelines for post-approval studies and clinical trials required to be conducted. The provision as written requires periodical evaluations, which we believe could impose unnecessary financial and time constraints on the agency. ***We recommend that the Committee clarifies that the evaluations should only be performed at the request of the FDA or the sponsor, or removes the word 'periodically.'***

### Title IV – Accelerating the Discovery, Development, and Delivery Cycle and Continuing 21<sup>st</sup> Century Innovation at NIH, FDA, CDC, and CMS

#### **Subtitle A – National Institutes of Health –**

Biocom strongly supports the provisions under this subtitle, which would streamline the operation and efficiency of the NIH, in addition to provisions mentioned previously (Title I, Subtitle K and Title II, Subtitles O and P). ***We also support the inclusion of section 4003-NIH travel, as allowing and encouraging NIH personnel to travel to attend conferences, workshops, and meet with stakeholders significantly improves employees' overall performance, productiveness, and consistency.***

However, Biocom is concerned that the authorization of additional funding for these programs as currently written is extremely limited and that funding will have to be pulled from existing programs within the NIH. NIH funding has been flat or declining in real-dollar terms over the past decade and remains below pre-sequestration levels, which has resulted in fewer grants and deferred opportunities to advance the development of new treatments and cures.

Biocom and our members believe that a much higher investment in NIH is needed to keep pace with 21<sup>st</sup> Century medicine, biomedical inflation, and global competitors. By supporting basic research, NIH provides a critical foundation of knowledge and technology



that drives private biomedical investment and innovation across the country. In addition, Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants have allowed small businesses and start-up companies to bring innovative ideas to commercialization. ***Biocom urges the Committee to authorize additional NIH funding to continue driving biomedical research and development.***

### **Subtitle C – Vaccine Access, Certainty, and Innovation**

Biocom supports provisions under this section, which would provide increased certainty and transparency with respect to the regulation of vaccines, and commends the Committee in its efforts to improve immunization practices and coverage.

### **Subtitle E – FDA Hiring, Travel, and Training**

***Biocom strongly supports the inclusion of this provision in the final legislation.*** We believe that the FDA should have the necessary resources to provide state of the art training to new employees, in addition to professional development opportunities to current personnel, including attending conferences and workshops. It is crucial for scientists and examiners to be appraised of new technologies and industry's always evolving needs and challenges, in order to bring the review and approval process to 21<sup>st</sup> Century standards. Biocom also supports providing the FDA with additional flexibility to set competitive salaries and attract former industry employees.

### **Subtitle F – FDA Succession Planning**

Biocom strongly supports this provision.

### **Subtitle H – Local and National Coverage Decision Reforms**

Biocom strongly supports this provision.

### **Subtitle I - Telemedicine**

Biocom recommends that the Committee addresses coverage for remote patient monitoring services, in addition to telehealth. A lack of coverage is indisputably one of the major barriers to the development of remote patient monitoring services and technologies. These modern technologies often reduce the need to physically visit a doctor's office or hospital, allowing patients to transmit health care information instantly in a home setting, thus containing costs, preventing the deterioration of conditions, reducing the frequency of visits to medical institutions, and ensuring the continuity of care. However, reimbursement restrictions deter providers from utilizing remote monitoring technologies in their

practices, which in turn limit patient access to these life-enhancing technologies and discourage investors from further financing innovative solutions.

***Biocom urges the Committee to address the need for coverage of evidence-based remote patient monitoring for chronic care, such as directing CMS to separately reimburse – i.e. unbundle - remote patient monitoring codes.*** Biocom and other stakeholders operating in the e-health sector submitted specific comments to the Energy & Commerce telehealth working group on February 26, 2015 detailing our suggested budget-neutral approach.

### **Subtitle P – Medicare Pharmaceutical and Technology Ombudsman**

Biocom supports this provision.

### **Subtitle T – Medical Testing Availability**

Biocom supports this provision.

## **Title V – Modernizing Medical Product Regulation**

### **Subtitle D – Medical Device Reforms**

Biocom strongly supports these provisions.

### **Note Regarding Funding**

Biocom commends the Committee on releasing such a comprehensive set of proposals to improve our innovation ecosystem - many of which we strongly support, as expressed throughout our comments. However, it is unclear to us how the programs and initiatives suggested by the Committee will be funded. Biocom is concerned that tasking the NIH, FDA, and other agencies with carrying out these new programs with flat funding levels will impose serious constraints on the agencies and the existing programs they administer.

Biocom does not support pulling funding from existing programs within the above-mentioned agencies and strongly supports authorizing additional funding for the provisions described in the discussion draft. We look forward to working with the Committee on these complex questions.

We appreciate the opportunity to provide feedback on behalf of our members and thank you for your time and diligence in examining our comments. Please contact Biocom's Associate Director of Federal Affairs, Laure Fabrega, at [lfabrega@biocom.org](mailto:lfabrega@biocom.org), for additional information or questions. We look forward to continuing working with you on this very important matter.

Sincerely,



Joe Panetta  
President and CEO  
Biocom



## COLLEGE of AMERICAN PATHOLOGISTS

---

March 3, 2015

The Honorable Fred Upton  
Chairman  
Committee on Energy & Commerce  
2125 Rayburn House Office Building  
Washington, DC 20515

The Honorable Frank Pallone  
Ranking Member  
Committee on Energy & Commerce  
2125 Rayburn House Office Building  
Washington, DC 20515

Dear Chairman Upton and Ranking Member Pallone:

The College of American Pathologists (CAP) is pleased to have the opportunity to comment on the Committee's legislative discussion draft entitled the "21<sup>st</sup> Century Cures Act" ("the Act"). The CAP, celebrating 50 years as the nation's leading authority in laboratory accreditation, is a medical society representing more than 18,000 physician members and the global laboratory community. It is the world's largest association composed exclusively of board-certified pathologists and is the worldwide leader in laboratory quality assurance. We welcome the Committee's efforts to reform the nation's regulatory processes in order to accelerate the discovery, development, and delivery of cutting-edge medicine and treatments for all Americans.

The CAP calls to the Committee's attention several recommended changes and areas for further discussion in the existing legislative draft. While our greatest concerns rest with the Act's efforts to reform the Local Coverage Determination (LCD) process and the current placeholder for the regulation of diagnostic Laboratory Developed Tests (LDTs), we take this opportunity to comment on the Act's recommendations for the development and use of Clinical Registries, the Physician Quality Reporting System (PQRS), EHR Meaningful Use and interoperability, and Telemedicine. The CAP looks forward to working with all stakeholders on these and other issues as the Committee works to improve healthcare outcomes for all Americans.

### **Title IV, Part 2, Subtitle H, Sec. 4161: Improvements in the Medicare Local Coverage Determination (LCD) Process**

The CAP is very pleased to see the Committee consider "ways in which the NCD/LCD process can work better for both the administration and those seeking coverage under the Medicare program." However, the CAP does not believe the Act, as currently drafted, goes far enough to reform the existing problematic process. We are increasingly concerned about the "black box" processes that drive coverage determinations, especially those that lack any meaningful and responsive dialogue between stakeholders – particularly those with relevant subspecialty expertise – and Medicare Administrative Contractors (MACs). In short, the current process is not what was envisioned in law nor is it what was intended in regulation. The current LCD process unnecessarily jeopardizes beneficiaries' health by limiting their access to care. We believe the following changes will increase transparency and boost accountability in the LCD process and remove unnecessary impediments to seniors' access to quality care:

- **Open Meetings** – The CAP recommends the Committee require that MACs hold open and public Carrier Advisor Committee meetings whenever a MAC proposes to limit or preclude coverage of services for Medicare beneficiaries. These meetings would be open to the public and on the record with minutes taken and posted to the MAC website. The gravity of limiting or precluding coverage for both beneficiaries and practitioners heightens the need for meeting transparency and the necessity of capturing that meeting in publicly accessible records. Requiring these increased levels of transparency will facilitate an improved forum for information exchange between MACs and interested parties, and will result in an openness that is glaringly absent from the current LCD process.



- **Release of Description of Evidence and Rationale** – The CAP supports the Committee's efforts to improve evidentiary underpinnings of LCDs. However, in order to facilitate a more transparent process where stakeholder input at open meetings can be used in the most effective manner, additional requirements are necessary. The CAP recommends the Committee require a MAC to include the rationale and all evidence considered not only in a final LCD, but at the outset of the process when a draft LCD is released. If this critical information is not provided until the final LCD, no meaningful exchange, criticism, or questioning can occur. Since the Centers for Medicare and Medicaid Coverage (CMS) intended the LCD process to be one predicated upon stakeholder exchange, permitting a MAC to hold the rationale and evidence they rely on to limit or deny coverage until the end of the process underscores how flawed this process has become.
- **Reconsideration** – Under current CMS requirements, a MAC's decision to impose an LCD is essentially unreviewable once the MACs make a decision on coverage. In order to be reconsidered, a petitioner is required to present new evidence. This means that erroneous decisions cannot be challenged and leaves open the very real possibility that appropriate coverage can be denied based upon a biased consideration of the evidence. In addition, reconsideration is made to the very MAC that finalized the LCD in the first place. An improved LCD process would permit a true secondary review of the evidence used by the MAC to deny or limit coverage. To achieve this end, the CAP recommends the Committee codify changes to the existing reconsideration process and remove the requirement for presentation of new evidence in order for an LCD to be reconsidered. The CAP also recommends that reconsiderations by interested parties be made to a CMS regional office rather than to the MAC, and that a petitioner be afforded a secondary appeal to the CMS Administrator.
- **Nationwide Coverage** – When a MAC, either in practice or by designation, is tasked by CMS with determining coverage for certain services or specialties, nationwide coverage decisions can be imposed through a back door process in which other MACs simply rubber stamp the LCDs issued by the originating MAC. This back door process allows CMS to evade undertaking the more rigorous National Coverage Determination (NCD) process and underscores the need to substantially strengthen the LCD process to include additional protections against its abuse. The rubber stamping of a MAC's LCD by other MACs can quickly become a de-facto National Coverage Determination. The CAP has very recently witnessed one MAC move to adopt the LCD imposed by another MAC and announce that it is predisposed to adopt the LCD prior to its consideration of the evidence. Further, we are concerned that the express mention of adoption of another MAC's LCDs in the Act will only encourage further expansion of this back door process for making national coverage determinations. Therefore, the CAP believes the Committee should include the following prohibitions in the Act: In no event shall CMS appoint a MAC, expressly or in practice, to establish determinations to be deployed on a nationwide basis. Further, MACs must independently consider the evidence for their LCD coverage determinations.

#### **Title II, Part 3, Subtitle J, Sec. 2161: Modernizing Regulation of Diagnostics**

The CAP reads this section of the Act as a placeholder for legislation altering the regulatory framework governing the approval of Laboratory Developed Tests (LDTs). Should the Committee choose to legislate in this space, we believe that any comprehensive framework for the regulation of LDTs must be written in such a way as to enhance, not interfere with, the delivery of potentially life-saving testing for patients, and that does not stifle medical innovation nor is overly burdensome on laboratories.



The CAP believes that any oversight framework proposed by the Committee must be consistent with how modern clinical laboratories provide patient testing. This includes being prudent in determining which LDTs are included in the proposed oversight. LDTs include a vast range of tests and test modifications, from trivial modifications of Food and Drug Administration (FDA) approved tests to proprietary tests that are performed in single laboratories using proprietary algorithms. This broad net includes some of the most innovative clinical testing being offered today, which is critical to providing information to physicians caring for patients. In 2009, the CAP outlined and shared with the FDA and other stakeholders its proposal for the rational oversight of LDTs. We continue to support that 2009 proposal, and we believe these features should serve as a blueprint to the Committee as it considers legislating in this space. For Congress to achieve its goal of accelerating the discovery, development, and delivery of cutting-edge medicine and treatments for all Americans, we believe any legislative proposal must:

- Include tiered, risk-based regulation that would focus oversight on the tests that currently have the least transparency and highest potential patient risk.
- Allow for evaluation of patient risk based on a laboratory's claims for the test and the potential for harm to patients of an incorrect or misinterpreted test.
- Provide for achievable and targeted FDA oversight of high-risk LDTs as we define these categories in our proposal.
- Provide assurance of both analytic and clinical validity of laboratory tests.
- Allow for continued CMS oversight of laboratory quality under Clinical Laboratory Improvements Amendments of 1988 (CLIA) for moderate- and low-risk LDTs as we define these categories in our proposal.
- Encourage coordination between the FDA and CMS to avoid duplicative or unduly burdensome requirements on laboratories.
- Promote innovation of new diagnostic and predictive tests.
- Protect the ability of pathologists to continue to bring life-saving testing to patients through the practice of medicine.

The CAP has unique insights into the benefits and risks presented by LDTs and the many practical issues surrounding their regulation. As medical specialists in the diagnosis of disease, pathologists have a long track record of delivering high quality services to patients through the practice of medicine. We have a keen interest in ensuring that our ability to provide high quality diagnostic services to patients and other physicians is not overly restricted. Moreover, as an accreditation agency, the CAP has oversight responsibilities in a variety of laboratory settings, from complex university medical centers to physician-office laboratories, covering a complete array of disciplines and testing procedures available in today's laboratory. Therefore, if the Committee decides to move forward on legislating in the LDT arena, we believe CAP's involvement is essential, and respectfully request that CAP's 2009 proposal serve as a blueprint for any legislation.



**Title II, Part 3, Subtitle F, Sec. 2092: Recommendations for Development and Use of Clinical Data Registries**

Currently, no quality clinical data registry (QCDR) exists that pathologists may use for reporting quality measures. The registries used by other specialties tend to be disease focused and designed to track patients over time. The CAP is exploring whether it can develop such a registry; however, challenges include the high cost of developing and maintaining a registry and the uncertainty around registry design that will meet future CMS requirements. CMS changes the requirements for its quality programs, including QCDR criteria, every year. Since it takes several years to develop a registry (in addition, CMS requires registries to be operational for at least a year before being used in its programs), anyone investing millions of dollars to develop a QCDR has no guarantee that it will meet CMS' future requirements.

Pathologists have fundamental challenges with QCDR design given their unique role in diagnostic medicine. Specifically, CMS requires QCDRs to include measures that assess patient's health outcome from clinical interventions. Pathologists diagnose disease and provide clinical diagnostic results that inform the patient and the clinician of the patient's current health status; however, pathologists do not routinely guide the subsequent care that determines the health outcome for the patient. The existing CMS definition of what constitutes a health outcome for patients is vague and open to wide interpretation. Given the significant investment necessary to establish a QCDR, the CAP believes Congress should require the Department of Health and Human Services (HHS) to provide medical specialty societies with greater certainty that the significant investments that each will have to make in building QCDRs will not be nullified through vague, imprecise requirements that change so frequently as to call into doubt the ability to meet future requirements. Therefore, we urge the Congress to require the Secretary to more specifically define how non-patient facing physicians, like pathologists, can meet the requirements for participating in outcomes-based registries.

**Title II, Part 3, Subtitle K, Sec. 2181: Interoperability**

The CAP reads this section of the Act as a placeholder for legislation designed to improve the interoperability of health information systems. The American Recovery and Reinvestment Act of 2009 allowed CMS to provide incentive payments to hospitals, physicians, and other eligible professionals who demonstrate meaningful use of certified electronic health records (EHRs). While pathologists are currently eligible to receive meaningful use incentive payments and penalties, they are largely unable to meet the program's requirements. For example, achieving certain objectives and reporting designated clinical quality metrics are inherently difficult for pathologists to meet, since our members have limited direct contact with patients and do not provide diagnostic information through an EHR. Rather, pathologists use sophisticated computerized laboratory information systems (LISs) to support the work of analyzing patient specimens and generating test results. These LISs exchange laboratory and pathology data with EHRs but are not recognized under CMS' meaningful use standard as a certified EHR technology.

CMS has acknowledged that pathologists and similarly situated professionals face significant barriers to meeting the current meaningful use requirements. CMS has granted pathologists a hardship exemption to the program's requirements in 2015, the first year of payment adjustments. In 2014, more than 90 members of Congress wrote CMS requesting that the exemption last for five years. Additionally, during the 113<sup>th</sup> Congress, landmark legislation to repeal the Sustainable Growth Rate (SGR) formula was crafted in a bipartisan, bicameral fashion that included language granting the HHS Secretary the flexibility to develop measures and activities that reflect the way pathologists and other non-patient-facing professionals practice. We believe the Act gives this Committee a unique opportunity to codify a five-year hardship exemption for pathologists and other similarly



situated professionals, or until modifications are made to the program so pathologists can comply with its requirements.

**Title IV, Part 2, Subtitle I, Sec. 4181: Telemedicine**

The CAP appreciates the Committee's recognition in its "sense of Congress" of licensure requirements when practicing across state lines. The CAP is opposed to legislation that would preempt or undermine state medical licensure requirements. We believe pathologists interpreting specimens, slides, or images sent through interstate commerce should be licensed in the state where the patient presents for diagnosis, with the exception of an intraspecialty consultation. We look forward to working with the Committee on this issue as it develops in the initiative.

The CAP welcomes the opportunity to work with the Committee to reform the nation's regulatory processes in order to accelerate the discovery, development, and delivery of cutting-edge medicine and treatments for all Americans.

Please contact Michael Brzica, Assistant Director, Legislation and Political Action, College of American Pathologists, at [mbrzica@cap.org](mailto:mbrzica@cap.org) or 202.354.7106 if you have any questions on these comments.

Sincerely,



Gene N. Herbek, MD, FCAP  
President, College of American Pathologists





March 13, 2015

The Honorable Fred Upton  
Energy and Commerce Committee  
U.S. House of Representatives  
2125 Rayburn House Office Building  
Washington, D.C. 20515

The Honorable Diana DeGette  
Energy and Commerce Committee  
U.S. House of Representatives  
2368 Rayburn House Office Building  
Washington, D.C., 20515

*Sent via e-mail: [cures@mail.house.gov](mailto:cures@mail.house.gov)*

RE: Comments on the 21<sup>st</sup> Century Cures Discussion Document

Dear Chairman Upton and Representative DeGette,

On behalf of the Colorado BioScience Association (CBSA), representing nearly 600 biotechnology, diagnostic, medical device, pharmaceutical and research institutions within the state, we thank you for the opportunity to provide comments on the discussion document released by the Chairman on January 27, 2015 in regard to the 21<sup>st</sup> Century Cures Initiative. Since the release of the discussion draft, the CBSA has conducted outreach to industry leaders and experts within our community to provide a thoughtful review of the proposals and their potential impact.

We commend you for your leadership on this initiative as we believe it is an important step to accelerate the discovery, development and delivery of cures for patients. The bioscience industry in Colorado is primarily comprised of small and early-stage companies, which plays a crucial role in the development of new innovative treatments. However, there is an important balance to ensure policy improvements do not impede innovation, especially for companies in these early stages.

In light of the discussion draft, we would like to take the opportunity to again request that Congress ensure stable and robust funding for both the FDA and NIH. Our industry is dependent on a strong and fully funded FDA, which in turn will allow the department to keep pace with the rapidly evolving biomedical and medical technology industries and help to make regulatory decisions in a timely and predictable manner. Similarly, our industry values the work of NIH and the cooperative spirit that has allowed industry and the government to achieve the common goal of finding treatments and cures for diseases. As the cost of the drug and device development process continues to increase, the funding for research through the NIH remains stagnant, subsequently leading to a lag between research and product development. Grant programs through the NIH SBIR/STTR programs are a lifeline to Colorado companies, allowing them to conduct early-stage research on novel therapies and devices. It is imperative that the NIH has sufficient funding in order to support the growing industry in our state and nationally. In order to implement the new proposals put forth within the 21<sup>st</sup> Century Cures Initiative, we encourage Congress to increase funding for FDA and NIH in order to support this important work while not pulling resources from other programs and activities.

CBSA is a partner to the national organizations representing the biotechnology, medical device and pharmaceutical industries and as such, our comments are generally in alignment with those submitted by AdvaMed, BIO, PhRMA and MDMA. A few key provisions have a specific impact on our industry in Colorado, and we wish to address these with you in the below comments.

Again, we are grateful for your efforts to date on this important initiative and welcome the opportunity to discuss these comments and provide additional input. Thank you for the opportunity to provide comments on the discussion draft of the 21<sup>st</sup> Century Cures Initiative.

Sincerely,



April Giles  
President & CEO

---

## **Colorado BioScience Association Comments**

### **Title I**

#### **TITLE I: Subtitle A**

- Ultimately, the patient is the beneficiary of the medical innovation which our industry is responsible for. We are encouraged to see the incorporation of patient experience data into the regulatory decision framework, but we believe the framework needs to be implemented objectively and incorporate the diversity of opinion. This provision should include specific guidance for how the structured risk-benefit framework will be enhanced and the associated objectives. In particular, the subtitle should acknowledge that individual patients' assessments of both risk and benefit for a particular therapy may vary greatly. Regulatory frameworks should account for this diversity to ensure that individuals have access to the most suitable therapies. Managing regulation to the "average patient" is not appropriate, depriving some of beneficial therapies (in the individual's perception) and potentially exposing others to undue risks, even with a physician's guidance.
- We believe "safe-harbor" language should be incorporated for patient engagement by industry that would be considered non-promotional.
- Industry should also play a role within the public workshops, methods development and data collection process.

**TITLE I: Subtitle B**

- Our community is generally supportive of this provision, but we believe the language should be broadened noting that a surrogate endpoint may not be a single biomarker, but a combination of several biomarkers.

**TITLE I: Subtitle C**

- Several companies in our community have been granted “Breakthrough Therapy” designation, which will help bring needed therapies to the market. We support the improvements to the Breakthrough Therapy designation, and the continued interest in speeding the development process for new therapies treating serious or life-threatening diseases.

**TITLE I: Subtitle D**

- Colorado is home to a number of successful early-stage vaccine technology companies; given that this is an important industry for the state both Title I Subtitle D and Title IV Subtitle C will directly impact these community members. The provision within Title I Subtitle D will require a company who utilizes the provision to make “donations” to the NIH and a patient assistance program. While encouraging additional funding for antimicrobial research is important, this requirement will set a new precedent which needs to be carefully thought out to ensure the provision does not become a disincentive for companies to bring new innovations to market.

**TITLE I: Subtitle E**

- Colorado’s medical technology sector has seen incredible growth over the past several years, with 23% growth in employment between 2007 and 2012. Establishing a new pathway which will allow breakthrough medical technologies to access a more expedient route to FDA approval and public insurance coverage will help bring needed medical products to the market more efficiently. While we await specific language on the process of obtaining coverage through the Centers for Medicare & Medicaid Services, we are strongly supportive of this proposal on behalf of our medical technology industry and believe it will help incentivize new research and product development. We believe the definition of “breakthrough technologies” should be applied broadly to incorporate new uses of existing technologies in addition to new products. We also look forward to reviewing the CMS Coverage language, and agree with the proposals submitted by AdvaMed on this issue.

**TITLE I: Subtitle G**

- During the 2014 Colorado Legislative Session, the issue of expanded access was debated in our General Assembly through House Bill 14-1281 entitled “Right to Try.” CBSA believes this issue needs to be addressed at the federal level. We are encouraged that provisions within Title I Subtitle G will convene a taskforce in an effort to improve the expanded access programs for investigational use of drugs. We also ask that careful consideration is made on how these policies are implemented in order to protect companies from litigation and burdensome paperwork if they are required to establish a policy on expanded access. Additionally, considerations need to be made in regard to companion diagnostics and tracking for safety and effectiveness.

**TITLE I: Subtitle I**

- Current regulations, guidance and enforcement practices by the FDA in regard to social media need to be updated. Increasingly, patients and caregivers seek to find health information on the internet, and companies developing medical therapies and technologies need to have the flexibility to communicate accurate and data-driven information on the internet and through social media channels. Title I Subtitle I is an important step which will allow for more flexibility in this communication, but consideration should be made in regard to secondary links and communication not in direct control of the company or manufacturer.

**TITLE I: Subtitle J**

- Oncology is one of Colorado's leading areas of research, and the Streamlined Data Review program has been a pilot program within the FDA's Division of Oncology Products. We are pleased to see the inclusion of this provision, as it would help to reduce regulatory burden for label expansions. As the pilot program continues within oncology, we will be eager to see if and when the FDA might potentially expand this program to more indications.

**TITLE I: Subtitle K**

- For Colorado, like many other states, funding for research and development is the largest challenge facing our industry. Incorporating efforts like the Cures Acceleration Network will help provide additional funding and resources for researchers who are identifying new indications for drugs and biologics and how they might impact high-need cures. We look forward to understanding more about this provision and the authorization of funding to support its intent.

**TITLE I: Subtitle L**

- Expanding incentives to reward innovation, especially for research and treatments targeted for unmet medical needs, is incredibly important. Granting a company an extended data protection period on a new treatment for an unmet medical need cannot only help a company to recoup the investments made during the research and development process but also allow them to reinvest those funds into additional research. We look forward to working with Senator Bennet on this provision, and believe it is an important step to generating new research on a variety of disease states.

**TITLE I: Subtitle M**

- Similarly to Title I Subtitle L, the ability to increase incentives for research can help spur new treatments in areas that might be overlooked. Incentivizing industry to improve existing therapies has the potential to identify new uses or develop better outcomes for current therapies. A clarification should be made as to whether or not this provision is inclusive of diagnostic testing or combination products which could improve the treatment, delivery, or diagnosis of existing therapies.

**TITLE I: Subtitle N**

- Similarly to Title I Subtitle L and Title I Subtitle M, this section will help to encourage companies with existing approved products to further understand how the therapy might treat rare diseases or conditions and potentially seek approval for additional indications under this provision. We

are supportive of this provision as we have several companies in our state currently conducting research on rare disease indications. We look forward to seeing the continued development of this provision in the legislative phase.

## Title II

### **TITLE II: Subtitle C**

- The work underway within regenerative medicine is incredibly exciting. Colorado is home to several companies involved in this research, including the Charles C. Gates Center for Regenerative Medicine and Stem Cell Biology at the University of Colorado Denver. We are encouraged to see updated guidance and clarity in regard to surrogate and intermediate endpoints for the accelerated approval of regenerative medicine.
- Additionally, we request there be a differentiation between the process required for pharmaceutical drug approval and stem cell or regenerative medicine treatment approvals. Allowing an expedited or streamlined review for regenerative medicine will help to more efficiently address current and emerging medical needs while also ensuring the US remain competitive in this research sector. We are happy to discuss this issue further, and connect you with relevant researchers and expertise within our community to address these concerns.

### **TITLE II: Subtitle D**

- While we appreciate the potential expansion of the Accelerated Approval pathway, there needs to be additional consideration on the technical language and policy implications of this provision. Specifically providing clarifications on the definitions and whether this provision will impact solely drug companies or also include medical technology and diagnostic companies.

### **TITLE II: Subtitle E**

- The digital health sector in Colorado has seen incredible growth in early-stage research and product development. As this industry becomes more advanced and mature, it is important that regulatory certainty is provided. We look forward to working with Senator Bennet on this provision and engaging this budding industry sector in our state as these provisions are developed into more formal legislation.

### **TITLE II: Subtitle F**

- As stated in our introduction, we work collaboratively with our national trade organizations. AdvaMed has produced a thoughtful response on the concerns this provision could have on the industry. We believe this provision needs to be thoughtfully crafted to develop a data sharing framework that is sustainable and will not impede on industry research and product development.

### **TITLE II: Subtitle G**

- Utilizing real world evidence can be an important factor in drug development, and also allow for a streamlined approval process for new indications and less burdensome route to achieving post-approval study requirements.

**TITLE II: Subtitle H**

- Colorado is home to a burgeoning diagnostic cluster, and provisions within Title II Subtitle H will develop an important pathway for diagnostics – particularly those oriented to long-term health outcomes and preventions. However, the process to allow CMS to use Coverage with Evidence Development needs to be well thought out, industry is currently working on additional recommendations for this section.

**TITLE II: Subtitle I**

- Current regulations for combination products at the FDA need to be more clearly outlined, this provision offers a step in the right direction to solve some of the current confusion. While we are encouraged to see the provision included, additional thought in regard to deadlines, disputes and process need to be better defined in an effort to provide clarity and consistency for this industry sector.

**TITLE II: Subtitle J**

- This provision will be important for Colorado and the companies within the diagnostic space. We look forward to seeing the language once developed and will be monitoring this provision and its potential impact on our community.

**TITLE II: Subtitle L**

- The majority of Colorado's bioscience industry has spun-out of our research institutions. The SBIR and STTR grants have provided critical funding to advance companies and research at its earliest stages. This provision is concerning for our industry. Companies rely on grants and early funding to advance their research and technology, at this stage in development it is counterintuitive for them to release data and information on their product development. While the language in the provision provides protection for trade secrets and confidentiality, the release of any sensitive information can put companies and their innovations at risk for further development.

**TITLE II: Subtitle M**

- Allowing greater access to protected health information could benefit further research and public health. Current ethical standards, protections within informed consent and the use or disclosure of a limited data-set need to be taken into consideration and not conflicted within this provision.

**TITLE II: Subtitle O**

- Colorado's research institutions on average collectively spin out 20 new bioscience companies annually, much of the early-stage research and studies are conducted by young researchers. We are supportive of this provision and encourage additional focus be placed on inspiring young scientists to engage in the bioscience field. We do however request a definition be included which would not solely base this provision on the age of a researcher, but to number of years in their respective research field. We also believe there should be additional allocations for this and other provisions as to not circumvent funding from other initiatives already in place at the NIH which supports small business and early-stage research.

## **TITLE II: Subtitle P**

- Additional funding for the NIH SBIR and STTR programs can help advance new cures, develop new research and elevate new products to the market. While we are supportive of the inclusion of Title II Subtitle P which will help incentivize research in high-risk areas, we believe this additional funding should be an additional allocation provided to the NIH in order to fulfill this provision so funding is not pulled from existing resources and programs important to industry.

## **Title III**

### **TITLE III: Subtitle A**

- Clinical trials are increasingly performed at multiple sites, so the broader utilization of a central Institutional Review Board can help in the modernization of clinical trials. Many of the additional details are left to the discretion of the Secretary of Health & Human Services, and we ask that these details are more clearly defined so industry can understand what future guidance and regulations might be forthcoming.

### **TITLE III: Subtitle B**

- CBSA supports the greater use of adaptive trials and Bayesian statistics. We are pleased to see the provision encourage more interaction between industry and FDA as proposals for protocols and non-traditional statistical approaches are identified.

### **TITLE III: Subtitle D**

- Colorado is home to a several companies seeking to develop drugs and devices specifically for the pediatric market. We are currently seeking comment from these companies to better understand the impact of this provision on their work and the reauthorization of the PREEMIE Act.

### **TITLE III: Subtitle E**

- Developing a clinical trial for pediatric populations can be difficult; establishing a global network to help facilitate these trials can potentially help bring new products for pediatric patients to the market. We look forward to the development of this initiative and further language.

## **Title IV**

### **TITLE IV: Subtitle A**

- As mentioned, the NIH plays a critical role in Colorado's bioscience ecosystem and the provisions set forth in Title IV Subtitle A will have a direct impact on our community. Primarily, CBSA is supportive of the steady growth of funding for the NIH including the growth of the SBIR and STTR programs which are essential to our industry. We support an increase to the NIH Common Fund,

but request that this increase should not come at the expense of current programs currently supporting small business and early-stage research.

- Additionally, we are supportive of the provision to establish a workgroup which will develop recommendations on how to streamline the grant process for researchers. We request the inclusion of industry in the workgroup to share their experiences directly.

#### **TITLE IV: Subtitle C**

- Colorado is home to several companies in both the research and product development stages of vaccinations. Section 4041 will help to provide more consistency and predictability for vaccine developers; however, expedited review for breakthrough therapies and for use during public health emergencies needs to be better defined. Potentially allowing for 30 days instead of 120 days after licensure.
- Most importantly, Section 4043 will help to update the current FDA procedures and standards for vaccine licensure which are antiquated. We request the timeline for this provision to be shortened to one year, as opposed to the two year timeframe called for in the draft.
- While communication between CDC and vaccine developers is important, Section 4044 could add a burden onto the CDC which may negatively impact their response during an outbreak. Ensuring the CDC is properly staffed to allow for more dialog with industry would be an important addition.
- Section 4045 should allow vouchers for tropical diseases to be transferable repeatedly like those in rare and pediatric diseases. Diagnostics for neglected diseases should also be provided a voucher.
- Under Part 2 both Section 4061 and 4062 will help increase adult immunization rates while also allowing industry a more predictable pathway for reimbursement which can help spur additional innovation.

#### **TITLE IV: Subtitle H**

- Most early-stage companies seeking reimbursement and coverage determinations will pursue local coverage first and then proceed to seek a national coverage determination. While we support improvements to the Local Coverage Determination process, we request that the language is thoughtful of how this provision will impact smaller companies as they bring new products to the market.

#### **TITLE IV: Subtitle M**

- Provider consolidation is a concerning issue amongst industry, especially for new companies trying to enter the market and compete against larger industry players. We appreciate the inclusion of this provision and taking a deeper look at how provider consolidations are impacted by payment policies.

#### **TITLE IV: Subtitle O**

- CBSA is supportive of the inclusion of the Accelerating Innovation in Medicine, which will allow medical technology companies to voluntarily be excluded from CMS coverage. These medical technologies will be billed to consenting patients and paid for out-of-pocket. The AIM Act will allow companies the option to access an additional pathway to market, while bringing new



medical products to patients in a more expedient manner. We request this provision to also be applicable to diagnostics.

#### **TITLE IV: Subtitle S**

- This provision will help ensure that physicians can continue to receive information and education related trainings on medical technologies and therapies, which has been discouraged through the implementation of the Sunshine Act. Both BIO and AdvaMed, our national trade association partners, have provided clarifying language which the CBSA is supportive of to ensure this provision is enacted as intended.

### Title V

#### **TITLE V: Subtitle D**

- This provision can help provide consistency and predictability in regard to the FDA's process for reviewing medical devices. Ensuring FDA reviewers and personnel are trained on "least burdensome means," expanding the definition of scientific evidence, and allowing for a third party quality system assessment mechanism are all issues important to our industry and we appreciate their inclusion. As this provision develops into formal legislation, we request that industry remain an active partner in the crafting of the language.

James C. Greenwood  
Biotechnology Industry Organization  
February 16, 2015

Dear Jim,

As per our discussion at the BIOCEO conference last week, below is a summary of the current issue we have with the existing DEA legislation and how it adversely affects our clinical progress in testing our experimental drug in Cystic Fibrosis and Scleroderma.

**Summary of Legislative Issue Currently Impeding Corbus' Clinical Progress**

Corbus Pharmaceuticals Inc is a Boston-based company dedicated to developing novel therapies for life-threatening rare diseases that currently lack adequate treatment and are, all too often, terminal. It offers a potential life-changing hope for tens of thousands of patients.

Our lead drug - Resunab™ - is about to enter Phase 2 clinical trials in Cystic Fibrosis and Scleroderma over the next few months under an IND with the FDA. The aim of these trials is to establish its mechanism of action and benefit to the patients. These trials are scheduled to take 18 months to complete with a combined budget in excess of \$15 million.

Resunab binds to a receptor in the body known as CB2. This receptor is part of the body's own endogenous signaling system called the "endocannabinoid system". This endogenous system exerts its actions on two organs: the brain (where it acts to alleviate pain) and the immune system (where it acts to reduce inflammation). There are numerous CB2-binding experimental drugs being developed by the pharmaceutical industry which target pain but none except ours which target inflammation. Unfortunately, phytocannabinoids (such as THC found in marijuana) also bind to CB2 (as well as to other receptors) and have a well-established psychotropic effect on the brain.

Resunab is a synthetic drug (it does not exist naturally), designed to have minimal penetration of the blood brain barrier, and thus to be devoid of any Central Nervous System (CNS) side effects. This unique property not only makes it a potent anti-inflammatory drug but also makes it the only CB2-binding drug with no CNS-activity. This has been demonstrated both pre-clinically and in Phase 1 in healthy volunteers.

**Our challenge is that Resunab, because of its binding to CB2 (due to its chemical structure) was automatically classified by the DEA as a schedule 1 controlled substance.**

In the US, drugs classified as schedule 1 are highly controlled by the DEA to avoid diversion and abuse. This means that to possess, transport and conduct research with a schedule 1 drug requires one to register with the DEA and keep careful, and costly,

controls on the storage and use of such drugs. The process of registering with the DEA to conduct research requires anywhere from 2-9 months depending on the time it takes for the local DEA field office and the head DC office to approve the request. Thus, every researcher, clinical trial site, analytical lab, and anyone else who needs to handle the drug, no matter how small the amount, needs to apply separately for DEA schedule 1 authorization before being able to work with the drug. This requires extensive periods of time to get researchers and clinicians registered to receive our drug to conduct research.

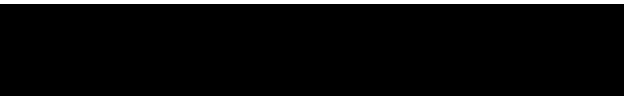
The process of registering with the DEA to manufacture a schedule 1 drug for clinical trials is even more complex and arduous, requiring months if not years to gain approval to manufacture the drug and months more to get approval for drug quota which is required every time a new batch of drug is to be manufactured. **This process not only slows down the drug development process but adds to the cost of developing drugs.** For example, it took our Contract Manufacturer four months to receive quota approval from the DEA to manufacture capsules for our clinical trials. **This delayed the filing of our IND and start of our clinical trials by at least six months.**

The designation of Resunab (a drug designed not to penetrate the brain and which has demonstrated minimal if any psychotropic effects in animals and humans) as Schedule 1 by the DEA is rendered even more absurd by the fact that **Resunab is not burdened with such designation in many of the other countries we will be conducting trials in including UK, Finland, France and other.**

You asked me to propose a solution to this problem, so it might be incorporated into the 21st Century Cures bill. I propose that the DEA be required to schedule all controlled substances at the research and clinical development stage (prior to FDA approval) at a classification no stricter than schedule 2. This way researchers and physicians who already are registered with the DEA can work with these substances without requiring additional licensing and quota. And those researchers and physicians who don't already have a controlled substance license can apply for a schedule 2 license which is much less time intensive than schedule 1. Also, manufacturers would not need a special permit and quota to make schedule 2 clinical trial materials. This would not only help biomedical research and the patients who can potentially benefit from these drugs, but also reduce the administrative burden on the DEA required for the management of schedule 1 controlled substances used for research and development.

Thank you for your offer to help. Please let me know how I can help move this along.

Best regards,

A solid black rectangular box used to redact the signature of Mark A. Tepper.

Mark A. Tepper, Ph.D.  
President & Chief Scientific Officer  
Corbus Pharmaceuticals Inc.



100 River Ridge Dr  
Norwood, MA 02062  
617-963-0104 (office)  
617-413-3020 (cell)  
617-663-6085 (fax)  
[mtepper@corbuspharma.com](mailto:mtepper@corbuspharma.com)  
[www.corbuspharma.com](http://www.corbuspharma.com)





March 2, 2015

The Honorable Fred Upton  
Chairman  
Energy and Commerce Committee  
House of Representatives  
Washington, DC 20515

The Honorable Frank Pallone  
Ranking Member  
Energy and Commerce Committee  
House of Representatives  
Washington, DC 20515

The Honorable Diana DeGette  
Energy and Commerce Committee  
House of Representatives  
Washington, DC 20515

Dear Chairman Upton, Ranking Member Pallone, and Representative DeGette:

The Cystic Fibrosis Foundation applauds your efforts to focus attention on research and development of new treatments for those Americans who are suffering from diseases with inadequate treatment options. We appreciate your desire to ensure that the research, regulatory, and reimbursement systems are fully responsive to all Americans who need new medical treatments.

Representatives of the Cystic Fibrosis (CF) Foundation have participated in 21<sup>st</sup> Century Cures hearings and roundtable meetings in Washington, DC and around the country. We are pleased to have been included in the extensive fact-finding process undertaken by the committee and to have the opportunity to comment on the discussion draft recently released.

### ***21<sup>st</sup> Century Regulatory Review***

The Food and Drug Administration (FDA) must immediately be ready for regulatory review of the drugs of the 21<sup>st</sup> Century, including precision medicine drugs. As we make progress in classifying disease by

#### **National Office**

6931 Arlington Road Bethesda, Maryland 20814  
(301) 951-4422 (800) FIGHT CF Fax: (301) 951-6378 Internet: [www.cff.org](http://www.cff.org) E-mail: [info@cff.org](mailto:info@cff.org)

genetic mutation, treatments will be targeted to those specific mutations. This discovery and development process will be complex and will raise regulatory challenges, as well. In order for FDA to be ready for this scientific and therapeutic development revolution, reviewers must be well-trained in the issues related to targeted, or precision medicine; they must be willing and able to reach across disciplines to obtain expertise related to a specific disease or therapy that they may lack; and they must be open to consultation with external experts who may possess that expertise.

The review of targeted therapies for small sub-populations of rare disease patients will raise many issues, including evaluation of “n of 1” trials, identification of appropriate endpoints for therapies that may provide significant benefit by preventing the progression of a chronic disease, and the evaluation of patient-reported outcomes for chronic disease patients.

The diseases themselves present complexities to regulatory review staffers. Each genetic mutation within a single disease may present specific disease traits, and reviewers will face obstacles to understanding and distinguishing the specific mutations and the appropriate targeting of drugs by mutation.

The ability of the agency to address the complexities of reviewing targeted therapies will rely significantly on the quality of the employees who are hired, trained, and retained by the agency. We also recommend strategies for consultation with outside experts to supplement and strengthen the expertise and skills of the agency staff.

We note that the current discussion draft does not yet include legislative language related to FDA hiring, travel, and training. In our opinion, successfully addressing the issues related to hiring and retention of quality FDA staff will determine the future of the agency and its ability to review precision medicines.

We recommend that the legislation address these issues in order to prepare an FDA workforce for the 21<sup>st</sup> century:

- Streamline the process for hiring FDA reviewers so that delays in hiring are eliminated and the leaders at FDA can promptly fill vacancies and hire reviewers with the skills and expertise necessary for complex product review.
- Address any obstacles – related to financial issues and conflicts of interest – that hinder the ability of review staffers to attend and participate in scientific and medical meetings.
- Provide resources for the training and mentoring of new reviewers, a process that may require additional agent FTEs so that experienced staffers can assume training responsibilities.
- Encourage flexibility in hiring, including placement of employees who will be employed part-time at FDA and part-time at the National Institutes of Health (NIH) so that FDA reviewers can continue research responsibilities or clinical care work that may inform their review work or provide them important background and knowledge related to new medicines.

The steps above are intended to provide flexibility to the agency to enhance its ability to hire and retain talented review staffers.

We also recommend a review of the regulatory science initiatives that have been undertaken by FDA and NIH to assess their effectiveness in the training and retention of reviewers. If those efforts have been useful, they should be continued and expanded. Such expansion may not require legislative action, but we recommend that this review be undertaken immediately and that the results inform the work of the committee.

### ***Consultation with External Experts***

During the debate on the Food and Drug Administration Safety and Innovation Act (FDASIA), the CF Foundation urged Congress to consider mechanisms for FDA review staffers to consult with experts outside the agency on topics related to the review of rare disease drugs. We have consistently maintained that the strength of the agency would be defined by its personnel, but we also thought that new drug review – including review of targeted therapies – would be strengthened if experts from outside the agency were consulted.

Section 903 of FDASIA -- Consultation with External Experts on Rare Diseases, Targeted Therapies, and Genetic Targeting of Treatments – requires the Secretary to maintain a list of external experts who might be consulted on review issues related to rare disease and genetically targeted treatments. These experts might be consulted if the Secretary “... lacks the specific scientific, medical, or technical expertise necessary for the performance of the Secretary’s regulatory responsibilities and the necessary expertise can be provided by the external experts.”

The “external expert consultation” provision of FDASIA also identifies specific issues on which external experts might advise the agency, including rare diseases, the severity of rare diseases, the unmet medical need associated with rare diseases, the willingness and ability of individuals with a rare disease to participate in clinical trials, an assessment of the benefits and risks of therapies to treat rare diseases, the general design of clinical trials for rare disease populations and subpopulations, and the demographics and the clinical description of patient populations.

External experts who would provide advice under Section 903 would do so as special government employees.

To our knowledge, the agency has not moved to develop and maintain the list of external experts and has not chosen to consult external experts on the subjects identified in FDASIA Section 903.

We believe that the need for external expert consultation of the sort we identified and articulated during the FDASIA debate still exists. As included by Congress in the user fee reauthorization, the agency controls the development and maintenance of a list of experts and also controls the decision to take advantage of external expert advice. We recommend that the committee reconsider the external expert consultation provision of the law and evaluate whether parties outside the agency should be permitted to request that the agency obtain external expert advice.

We recommend that product sponsors and patients be allowed to request that the agency consult with outside experts. The final decision to seek such advice would still be at the discretion of the agency, but other parties could make a recommendation that advice be obtained. In our experience, the topics related to rare diseases and rare disease therapies that are identified in the law are still topics on which FDA often needs additional information and advice. However, the agency does not typically seek that information and advice.



### ***Patient-Focused Drug Development***

We are pleased that the committee wishes to emphasize patient-focused drug development strategies. The discussion draft raises questions for us about how patient experience data will be used in regulatory review. The draft indicates that these data will inform the risk and benefit consideration, but it is not clear to us in concrete terms how that will be accomplished.

We recommend three ways in which patient input regarding disease burden, unmet medical need, management of a complex chronic condition, and quality of life considerations can inform the regulatory review process.

First, the patient-focused drug development meetings that were authorized by FDASIA should be refined and continued. Although there has been no meeting focused on cystic fibrosis and we realize the meetings are ongoing, we can offer some advice about the meetings. We believe that the meetings should be structured so that they address issues of disease burden, unmet medical need, and the burden of chronic care management. In the case of CF, we believe that conveying the ongoing daily therapy burden and the progressive nature of the disease will serve to educate drug developers and regulatory reviewers about ongoing therapy needs and how discovery and development efforts may address those therapeutic needs. We also advise that review staff be involved in these meetings, from planning through attendance and consideration of recommendations from the meetings. This is the optimal means for ensuring that the meetings have a connection to and inform the drug review process. We would also note that patient quality of life data, if collected and analyzed appropriately, might also be used in the regulatory review process. These data may be especially useful in assessment of therapies for progressive chronic diseases, including cystic fibrosis. We discuss this issue below.

Second, we recommend that the external expert consultation provision that we discuss above be utilized to obtain advice about drug development and review from patients and patient advocates.

Finally, we urge that patient-reported outcomes be considered during the drug review process. To make this a viable option, the agency must move to approve patient-reported outcome instruments. We urge that they do so without delay so that PRO data can be responsibly considered during drug review.

### ***Real-World Evidence***

We note with interest the inclusion of a provision in the discussion document that would permit sponsors to submit so called “real-world evidence” to support a new indication of an approved drug or to satisfy post-approval study requirements. The CF Foundation has for many decades supported a patient registry that collects important data about CF patients, their disease, and the treatments they receive. The data in this registry might be the type and quality that the discussion draft anticipates would be utilized in the regulatory review process.

We also note that the terms for utilizing real-world data will be established through a guidance developed by FDA. We urge that the legislation make clear that real world evidence shall be utilized in a review process that is data-driven and that the agency be encouraged to set standards for real-world evidence that will reassure patients that FDA-approved products are safe and effective.

### ***Sharing, Accessing, and Using Health Data***

The CF Foundation is enthusiastic about the potential for clinical trials, clinical care, claims, and other health care-related data to be utilized to improve drug discovery, development, and delivery. As discussed above, the Foundation has been a pioneer in the development and utilization of a CF patient registry.

As the committee looks at ways to improve the sharing and utilization of health data, we urge that your work be guided by a few simple principles: 1) patient privacy should be protected and patient and family trust in the use of their data should be maintained, 2) privacy protections should be commonsense approaches and should not be unreasonably bureaucratic, and 3) current systems and experiments in data collection and sharing should not be undermined by well-intentioned efforts to improve such sharing. We are aware of many entities – research foundations, academic health centers, medical professional societies, and pharmaceutical companies and consortia of companies – that are designing and executing “big data” projects. We urge that committee efforts to regularize and capitalize on these efforts not thwart their progress and creativity. We urge this caution on behalf of the Foundation and its patient registry efforts as well as others who are innovators in this area.

### ***Single IRB Review***

The CF Foundation supports a Therapeutic Development Network, or TDN, that links clinical research sites across the country and provides centralized data analysis services. The TDN has been a critical element in the success of the CF Foundation in therapeutic development. We are proud that we have brought efficiencies to many aspects of the clinical trials process, from patient accrual to data analysis at the end of trials. Duplicative institutional review board (IRB) review of trials has persisted as an inefficiency in our trials process.

We are pleased that the committee is directing attention to the issue of IRB review. In general, we support the movement toward single IRB review in multi-site trials. We urge that a single IRB used in this situation have the capacity to consider so-called “local issues” as well as the special needs of vulnerable populations.

### ***ACE Kids Act***

We commend the committee for attempting to meet the needs of children with complex medical conditions through inclusion of the Advancing Care for Exceptional (ACE) Kids Act in the discussion draft. We understand the pressing health care needs of children with complex medical needs, as many individuals with CF fit in this category. We are also well aware of the obstacles to quality care that these

children may encounter, including restrictive coverage and payment rules and limitations on care networks.

We are concerned that the solution of the ACE Kids Act, which would rely on children's hospital-based networks of care, would have the unintended consequence of creating new and different barriers to care for certain children with complex medical needs. For example, children with CF depend on a CF care network that includes hospitals, academic health centers, and other providers across the country. The networks that are anticipated by the ACE Kids Act are not consistent with the outstanding system of care that already exists for CF care. We encourage the committee to remain focused on addressing the access issues confronted by these children.

### ***The FDA Review Process***

We understand the interest in eliminating inefficiencies and streamlining the timeframe for regulatory review so that new products reach consumers at the earliest possible time. However, the drive to speed the regulatory process must be accompanied by efforts to protect the quality of regulatory review. It is critically important that individuals with CF and others with serious and life-threatening diseases can trust that the drugs they are prescribed are safe and effective and that FDA has reviewed data that support such findings.

It is most important that patients and their health care providers are assured that FDA review is rigorous and is based on thorough evaluation of safety and efficacy data. However, it is also important that third-party payers trust the FDA review process. We are concerned that third-party payers are considering determinations related to the "reasonable and necessary" use of a new drug that veer toward a full-fledged evaluation of the safety and efficacy of a new product. This approach will at the very least serve to slow patient access to new therapies, if payers undertake to effectively repeat an FDA review process they consider inadequate. There are also risks that such payer reviews will result in coverage standards that will seriously hinder patient access to new therapies, if such payers believe that FDA review is inadequate and that they must reconsider safety and efficacy data.

### ***Resources to Support a 21<sup>st</sup> Century Drug Development and Review Process***

We urge that the Congress make available the resources that FDA will require to be a 21<sup>st</sup> century regulatory agency. We have been mindful in our recommendations not to layer significant new responsibilities on the agency. However, we note that the hiring, training, and travel recommendations we have made will be accompanied by some additional cost to FDA. To make these recommendations meaningful, they must be resourced. The same is true for other new responsibilities that the committee would propose for FDA.

There are some situations in which the National Institutes of Health has provided certain core facilities and processes to foster translational research, and those successful efforts might be considered and expanded. For example, NIH has brought together diverse parties – foundations, academic researchers, and industry – to screen compounds in multiple libraries and identify targets for drug development. This

has occurred in the case of nontuberculous mycobacteria and other “superbugs” as well as in other disease areas.

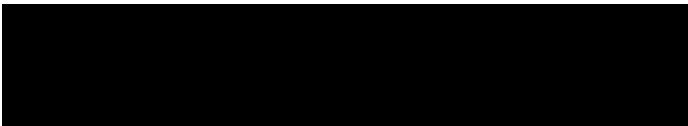
These are important models in which NIH has leveraged its central role in biomedical research to improve efficiencies and address duplication in translational research, bring important resources and leadership to under-resourced areas, and foster collaboration.

We recommend that existing programs, including but not limited to the National Center for Accelerating Translational Science, the Cures Acceleration Network, the Reagan-Udall Institute, and others (some established by legislative action and some by administrative action), be evaluated carefully to ensure that they meet the standards of fostering collaboration, accelerating research, and addressing inefficiencies and duplication in the research process. Existing programs should meet those high standards, and new efforts should be designed to meet them, too.

We offer a caution about the number of reports, commissions, and panels that are included in the discussion draft. FDA would be challenged to honor the reporting and advisory panel requirements in the discussion draft without new resources. Even if Congress determines that it will provide adequate resources for the agency to meet all of these new reporting requirements, we question if that is the best investment of new resources. As the legislative drafting process moves forward, we urge that all of the reports, commissions, and panels be rigorously evaluated before being included in a final legislative draft.

We appreciate the opportunity to comment on the discussion draft and look forward to additional discussions regarding 21<sup>st</sup> century cures.

Sincerely,

A large black rectangular box redacting the signature of Robert J. Beall.

Robert J. Beall, Ph.D.  
President and Chief Executive Officer

As the world's largest academic research organization, the Duke Clinical Research Institute (DCRI) mission is to develop and share knowledge that improves the care of patients around the world through innovative clinical research. DCRI is unique in the clinical research industry, as it unites the clinical expertise and academic leadership of a premier teaching hospital with the full-service operational capabilities of a major contract research organization. DCRI leaders are some of the world's foremost authorities on the science, study, and application of clinical research, making them uniquely positioned to understand the operational, financial, and regulatory implications of numerous project designs, to the great benefit of our patients.

The Pediatric Trials Network (PTN), led by Dr. Daniel Benjamin at DCRI and funded by the National Institutes of Health (NIH), is an international consortium of 160 clinical research sites cooperating in the design and conduct of pediatric clinical trials to improve health care for the youngest patients. Similar to the 21<sup>st</sup> Century Cures finding that, among the 10,000 known diseases, there are treatments for only 500, nearly 75 percent of all drugs used today do not have Food and Drug Administration (FDA) labeling for use in children. With the support of congressional leadership and the experience of the PTN, we can change the practice of medicine for children in this country and potentially in the rest of the world.

We appreciate the thoughtful approach that has been taken with the 21<sup>st</sup> Century Cures initiative and welcome this opportunity to share perspectives that will help you achieve your goal of accelerating the pace of cures in America. The comments attached represent feedback on several provisions in the discussion draft. Because the PTN has experience in the successful operation of a national pediatric clinical research network supporting unmet pediatric research needs, we urge you to consider our strengths and the federal investments already made when continuing your work refining this draft legislation. The PTN is eager to work with you in bringing pediatric research into the 21<sup>st</sup> century.

We support the Committee as it continues its important work and hope you will call on the DCRI if we may be of further assistance.

CONTACT:

Catherine Liao  
Assistant Director  
Office of Government Relations  
Duke University Health System

[Catherine.Liao@duke.edu](mailto:Catherine.Liao@duke.edu)

(919) 416-8913 (desk)

(919) 357-5692 (mobile)

## The history of pediatric medicines in clinical practice

Children have long been “therapeutic orphans” due to a combination of factors including: 1) ethical concerns; 2) lack of pediatric clinical trial expertise; and 3) economic incentives. In 1977, the American Academy of Pediatrics took a stand on this by issuing a statement that not only was it ethical but also imperative that drugs *used* in children be *studied* in children under controlled circumstances. There was insufficient impetus for drug manufacturers to take up this challenge so that, over the next 20 years, only a quarter of the drugs used in this country developed some form of labeling for pediatric use. Changing a drug’s label was solely within the manufacturer’s control. This is not unique to the laws in the United States; throughout the rest of world, only the innovating company has standing to propose a change the label of its drug.

Congress intervened in 1997 via the FDA Modernization Act by offering a special period of marketing exclusivity for innovators of drugs for pediatric populations. Subsequent legislation further incentivized -- then mandated -- pediatric research for drugs with a substantial use in pediatric populations. While the focus of much of the legislation was on new drugs, the 2002 Best Pharmaceuticals for Children Act (BPCA) had a significant impact on the pediatric drug research by allowing someone other than the drug manufacturer to initiate a change in drug labelling for existing (“off patent”) medicines.

The BPCA authorized the Secretary of the US Department of Health and Human Services, through the Director of the NIH, in consultation with the FDA Commissioner and pediatric research experts, to list approved drugs for which pediatric studies were needed and to assess their safety and effectiveness. Study requests on the priority drugs are then developed through collaboration with NIH, FDA, and other organizations. The NIH submits a proposed pediatric study request to the FDA, describing the clinical trials needed to improve pediatric labeling. The FDA then issues a written request for the study to the manufacturer and, if the manufacturer does not respond, the NIH can go forward with conducting this research.<sup>1</sup> The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) was delegated the authority and responsibility to establish and conduct these pediatric drug development activities. This was the genesis of the PTN.

## The Pediatric Trials Network

The PTN is funded through a contract with the NIH that provides up to \$95 million over a seven year period (2010 to 2017). The work of the PTN is led through a collaboration between the NICHD and the BPCA program, and the Duke Clinical Research Institute (DCRI), the world’s largest academic research organization.

PTN operates through five core disciplines chaired by clinicians and pharmacologists from key collaborating institutions. The core groups are: Clinical Pharmacology, Pharmacometrics, Safety and Ethics, Devices, and Mentorship. PTN has principal investigators located at 15 institutions

---

<sup>1</sup> The BPCA enacted in 2002 originally required the preparation of a list of approved drugs for which pediatric studies were needed to assess their safety and effectiveness. The 2007 reauthorization of the law changed the specifications from an annual list of approved drugs to a list, revised every three years, of priority study needs in pediatric therapeutics, including drugs or indications.

across the United States and currently has 160 research sites in its network. While PTN is now based predominately in the US, it also has clinical trial sites in the United Kingdom, Canada, Singapore, and Israel.

The chair of the PTN and its principal investigator is Danny Benjamin MD, PhD, MPH, Professor of Pediatrics at Duke University and faculty associate director of the DCRI. Between 2001 and 2014, Dr. Benjamin and his research teams enrolled more infants in off patent anti-infective therapies under an Investigational New Drug (IND) application than all other academic medical centers, pharmaceutical companies, and worldwide government agencies *combined*.

**Dr. Benjamin's experienced team and the lessons learned in establishing and successfully running the PTN over the last five years can offer a tremendous advantage to the successful implementation of the 21<sup>st</sup> Century Cures proposals for improving pediatric medicine in the US and worldwide.**

#### Shared objectives of 21<sup>st</sup> Century Cures and PTN

We are grateful for congressional support in prioritizing the study of pediatric medicines. The inclusion of pediatric research in the 21<sup>st</sup> Century Cures discussion draft has energized the researchers of the PTN.

Among the innovations in research that have been, or are currently being, spearheaded by the PTN are: access to data, federated oversight of research by centralized institutional review boards, master contracts for rapid site start up, use of master protocols, multi-arm pharmacokinetics/pharmacodynamics and safety studies, use of novel pediatric dosing optimization, use of statistical methods to reduce the number of children unnecessarily included in clinical trials, obesity dosing, and premature infant dosing.

**What that means to the 21<sup>st</sup> Century Cures initiatives is that there currently exists the architecture, knowledge, and determination within the PTN to bring the 21<sup>st</sup> Century Cures proposals to realization promptly and efficiently.**

#### National Pediatric Research Network

Subtitle D, Section 3041, would amend legislation enacted in 2013 to mandate, rather than suggest, the establishment of a National Pediatric Research Network. Per the statute, the network may be comprised of "the pediatric research consortia." These consortia are made up of public or private nonprofit entities that conduct or support basic, clinical, behavioral, or translational research to meet unmet needs for pediatric research. Each consortium is to be formed from a collaboration of cooperating institutions and coordinated by a lead institution or institutions.

**Upon enactment of this provision, there would be no need to start from scratch in developing a national network because it already exists. Due to the established infrastructure of the PTN, the time to site contract execution, time to IRB approval, and time to first patient enrolled are reduced. By extension, early achievement of these critical clinical trial milestones reduce costs. The PTN also actively invites new researchers to join**

**the PTN and has in place a process through which new researchers and research proposals may be submitted and vetted. Through the PTN, a “national” pediatric research network can only grow and grow expeditiously.**

Further, the PTN has proven itself to be a careful shepherd of its funding. The PTN not only successfully conducts research; it does so on time and on budget. PTN is able to this because of the network teams it has put together, its use of a master contract, and a steady stream of studies allocated to research sites so that site teams can remain intact rather than be continually disbanded and re-formed due to the ebb and flow of projects.

While all clinicians support the objective of pediatric research, in reality it is not easy to get top-tier researchers interested in conducting this type of very small trial. Research in pediatric populations is challenging, and as the age of the population decreases, the difficulty in conducting the research increases exponentially. PTN has engaged the interest of leading researchers in this field and offers the collaborative and collegial environment required to keep them invested. One of PTN's core disciplines is mentoring young researchers, to ensure that the caliber of researcher currently within PTN can continue as the network grows. **Under the PTN, more than 10 trainees (physicians and pharmacists) have either received advanced training in pediatric pharmacology/drug development, have secured intra- or extramural funding in pediatric research, have led clinical trials, and/or have collaborated with academic institutions nationally.** Further, PTN is actively involved in the support of young researchers, including through its mentorship program and through its ability to link participation in the PTN to the salary support provided by a young researchers K23 award (i.e., a Mentored Patient-Oriented Research Career Development Award). **This training track record in pediatric pharmacology/drug development is unprecedented.**

It has taken PTN five years and countless hours of active engagement with interested parties throughout the research world to build this foundation. **We urge you to build on this existing infrastructure rather than use additional federal resources to recreate a new but similar network.**

#### Global Pediatric Clinical Trial Network

Subtitle E, Section 3061 would support a sense of Congress that NIH should support a global pediatric clinical trial network. The section proposes that this be done through the allocation of grants awarded to entities that participate in the global pediatric clinical trial network to supplement the salaries of young researchers. The section also would encourage FDA to engage the European Medicines Agency (EMA) and other foreign regulators to encourage and facilitate participation in the global network.

As you may know, a global pediatric clinical trial network already exists. The EMA established in 2008 the European Network of Paediatric Research (Enpr-EMA), which includes institutions from member states within the European Economic Association as well as organizations in Japan and Canada. One of the goals set in the Enpr-EMA's 2014 annual workshop was to initiate international collaboration with clinical pediatric research initiatives in the US. **Because the PTN is the leading pediatric initiative in the US and is already actively engaged in pediatric**



**research in countries outside the US, the PTN intends to be the first US member of Enpr-EMA and welcomes collaboration with its worldwide counterparts.**

### Data Sharing

Four different sections of the 21st Century Cures discussion draft (Subtitles F, H, L and M) address data sharing in some fashion. Data sharing is of extreme importance to researchers and of particular importance to the PTN. The PTN has been investigating the use and effect of medications in children and infants for five years, which results in a lot of data. We are ready and eager to share the PTN's data, but we have not received any requests to date. PTN researchers have published over a dozen manuscripts, all of which are accessible by researchers, yet no one has yet asked for data underlying any of these manuscripts.

We believe this is due primarily to two difficulties frequently encountered by researchers in attempting to access data: not knowing what is needed to get the data and not knowing up front exactly what data will be received. The PTN intends to preemptively remove these barriers by putting all of its data on the PTN website. By cataloging what data exists and clearly enumerating the request process, any researcher anywhere with internet access will be able to view the PTN "catalog" and determine if what they need exists there and how to go about getting it.

Subtitle M of the 21<sup>st</sup> Century Cures discussion draft would be of great benefit to this data access. By removing the barriers to research use of protected health information (PHI) among covered entities, your proposal would put academic research data on equal footing with what is collected and used by private industry. **The additional provision allowing a one-time authorization through which a person can grant access to their PHI for ongoing future research purposes would provide a continuous trove of data upon which research can build.**

Anonymous data is not useful in supporting changes to clinical practice: at least some medical history from which the data results is necessary. This can be of particular importance in pediatric medicine. Of the 100 most commonly used medicines in a neonatal intensive care unit, 87 of them are not labeled for pediatric use, and of the ones that are labeled, most are being used at different doses, for different indications, or in different populations than stated on the labels. The medical records of these infants can be of great value to qualified researchers *if* the researcher is allowed to access and use the information. We believe that parents would be willing to give permission to use their child's medical information for research if it were a less intrusive process, i.e., consent that can be given once and last until withdrawn rather than have to be reauthorized at every clinical visit. Most people realize that even if there is no immediate benefit to themselves or their children, medical research will benefit them or others in the future.

Finally, we find Subtitle H of the 21st Century Cures discussion draft, "Facilitating Responsible Communication of Scientific and Medical Developments," intriguing. This section is "to be provided" at a later date, allowing for speculation on what it may eventually propose. One speculation has been that this section would introduce a safe harbor for the communication of off-label uses of medication. In the absence of evidence-based practices, off-label use may be a

physician's sole recourse. While providing some way for physicians to share information on off-label use may have some value, the real answer lies in promoting the research needed to establish the scientific basis for this use.

Another possible topic ripe for address in Subtitle H would be exploring ways in which regulatory authorities can obtain and act upon all available scientific evidence when making decisions regarding a medicinal product. For example, it is only through the special processes afforded by the BPCA that the academic research done by PTN can be used to support a label change for a pediatric product here in the US. This evidence is not available for similar use by Health Canada, Australia's Therapeutic Goods Administration, or other regulatory agencies unless it is submitted by the product sponsor as part of its labeling support.

Even here in the US, if the special processes established through the BPCA are not applicable, the data upon which the FDA bases its decisions is controlled by the marketing authorization applicant. This may, and frequently does, include the results of academic research, but it is up to the applicant to make that determination. This cheats academic research of attaining its true value. As an independent and neutral party, the academic researcher is motivated by finding the answer: good, bad or inconclusive. It makes scientific sense to elevate the results of the research done within the academic and non-profit community to carry the same weight as that of industry sponsors for the purposes of motivating regulatory authority's decisions. This is not a question of debating scientific merit; it is merely a question of standing, something that is unquestionably within congressional purview.



# FASEB

Federation of American Societies  
for Experimental Biology

## Representing Over 120,000 Researchers

301.634.7000  
www.faseb.org

9650 Rockville Pike  
Bethesda, MD 20814

March 4, 2015

The Honorable Fred Upton  
U.S. House of Representatives  
Energy & Commerce Committee  
2125 Rayburn House Office Building  
Washington, DC 20515

The Honorable Diana DeGette  
U.S. House of Representatives  
Energy & Commerce Committee  
2322A Rayburn House Office Building  
Washington, DC 20515

Dear Chairman Upton and Ranking Member DeGette:

The Federation of American Societies for Experimental Biology (FASEB) comprises 27 scientific societies, collectively representing over 120,000 biological and biomedical researchers. We thank the Energy and Commerce Committee for focusing its attention on the discovery process and your efforts to ensure that we can take full advantage of the advances the country has made in science and technology. The opportunities for progress have never been greater, yet major obstacles, including funding constraints imposed by the Budget Control Act, are preventing us from achieving all of the possibilities available today.

In January, FASEB released an analysis of the threats to continued progress in biological and medical science research. *Sustaining Discovery in Biological and Medical Science: A Framework for Discussion* examined the challenges facing researchers and presented a series of recommendations to alleviate them. The FASEB report documented how shortfalls in federal funding and rising regulatory costs have constrained research budgets. At the same time, scientific opportunities have expanded, the research workforce has grown, and thus, more individuals are seeking support for research projects. These opposing trends have resulted in an increasingly unstable research enterprise, delaying scientific discovery.

FASEB appreciates the opportunity to comment on the discussion draft of the 21<sup>st</sup> Century Cures legislation. We are, however, disappointed in the sections of the 21<sup>st</sup> Century Cures proposal that are focused on the National Institutes of Health (NIH). The discussion draft lacks a comprehensive statement about the fundamental problems affecting the United States research enterprise as articulated by recent reports and papers including the FASEB *Sustaining Discovery* report, “Restoring the Foundation: The Vital Role of Research in Preserving the American Dream” (Norm Augustine and Neil Lane, American Academy of Arts and Sciences), and “Rescuing U.S. Biomedical Research From Its Systemic Flaws” (Bruce Alberts, Marc Kirschner, Shirley Tilghman, and Harold Varmus). In addition, the NIH provisions fail to provide a coherent set of recommendations, do not address the major issues slowing research progress, and do not incorporate important corrections to current procedures.

Our concerns cover the following four basic themes: redundancy with existing regulations; omission of key sections; micromanagement of agencies that could hinder future progress; and contradictory and superfluous provisions.

---

The American Physiological Society • American Society for Biochemistry and Molecular Biology • American Society for Pharmacology and Experimental Therapeutics  
American Society for Investigative Pathology • American Society for Nutrition • The American Association of Immunologists • American Association of Anatomists  
The Protein Society • Society for Developmental Biology • American Peptide Society • Association of Biomolecular Resource Facilities  
The American Society for Bone and Mineral Research • American Society for Clinical Investigation • Society for the Study of Reproduction • The Teratology Society  
The Endocrine Society • The American Society of Human Genetics • International Society for Computational Biology • American College of Sports Medicine  
Biomedical Engineering Society • Genetics Society of America • American Federation for Medical Research • The Histochemical Society • Society for Pediatric Research  
Society for Glycobiology • Association for Molecular Pathology • Society for Free Radical Biology and Medicine

## **There is extensive redundancy with existing laws, rules, and policies**

Overlapping and redundant regulations increase the cost of research and decrease the amount of time scientists spend conducting actual research. Indeed, the Federal Demonstration Partnership found that faculty in the biological, health, and agricultural sciences spend more than 40 percent of their grant-funded time on administrative tasks.<sup>1</sup> Patchwork regulations also make it challenging for institutions and investigators to ensure full compliance. Several items within the proposed bill duplicate existing regulations and practices.

Section 2081 amends the Public Health Service Act to establish a publicly-accessible database for clinical trial registration and results. However, Section 801 of the Food and Drug Administration Amendments Act (FDAAA) mandated the creation of such a database in 2007 ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)).

Greater data sharing for NIH-supported projects is proposed, in Section 2201 of the draft bill. A 2013 memorandum issued by the Office of Science and Technology Policy (OSTP) (“Increasing Access to the Results of Federally Funded Scientific Research”) already requires research agencies, including NIH, to develop plans to increase public access to research data. This memorandum also provides a comprehensive list of circumstances of when mandatory data sharing is not required.

A database for re-evaluation and re-use of clinical research data could enhance scientific rigor and minimize duplicative research efforts. However, the database described in Section 2082 would have limited value due to the small number of data categories that can be shared without risking participant privacy. Technological and scientific advances continue to expand the types and combinations of data that can be used for re-identification. Alternative methods to make data available for analysis while still protecting privacy are being developed by NIH and the Agency for Healthcare Research and Quality; to maximize benefit, databases require the flexibility to take full advantage of improved methods and practices.

There are several programmatic redundancies established within the draft bill that may increase inefficiency and lead to additional overlapping and duplicative regulations. For example, the Innovative Cures Consortium’s mission, as established in Section 2001, is remarkably similar to that of the National Center for Advancing Translational Sciences. Also, Section 4002 establishes a working group to address administrative burden in biomedical research. Several federal advisory groups, including the National Science Board and the National Academies of Sciences, are already addressing this issue. Therefore, a new working group is not warranted. This working group is also directed to provide recommendations on restructuring, streamlining, and simplifying grant proposal submission at NIH. Currently, however, NIH has three separate groups examining this very issue (the Scientific Management Review Board, the Center for Scientific Review, and the Advisory Committee to the Director).

---

<sup>1</sup> **Schneider SL, Ness KK, Rockwell S, Shaver K, Brutkiewicz R.** *Federal Demonstration Partnership 2012 Faculty Workload Survey Research Report*. April 2014.

### **Several important sections are missing from the bill text**

Several sections of the 21<sup>st</sup> Century Cures draft legislation, including those that address work-related travel of federal researchers, regulation of diagnostics, and proposed authorization levels, have been left blank. These sections could significantly impact the research enterprise. Therefore, it is critical that the text be provided to stakeholders as soon as possible so that the implications of the proposed legislation can be evaluated *in toto*.

Travel restrictions placed upon federal researchers continue to be an area of major concern. Recent policy changes have disrupted the research programs within several agencies. Federal scientists face more barriers to attend professional meetings which are essential for sharing research findings and identifying new opportunities for collaboration. Some federal clinical researchers have encountered difficulties attending continuing education courses necessary to maintain licensure. Unfortunately, the text addressing travel of NIH and Food and Drug Administration (FDA) employees is omitted from sections 4003 and 4101 and, as a result, the bill does nothing to correct the problems caused by the restrictions on travel.

The title of Section 2161 suggests that it may include regulation of Laboratory Developed Tests (LDTs). Based on the responses to the FDA's proposed regulatory framework for LDTs, it is evident that establishing regulation that both ensures quality of the tests and promotes innovation will be challenging. Again, the bill text for this section was omitted.

FASEB has described the benefits of multi-year budget authority for research agencies, including NIH, in its *Sustaining Discovery* report. Under the current yearly funding authority, the frequent delays in passage of appropriations bills compress the time available for funding decisions by NIH. In a typical year, NIH is forced to return \$300 million to the Treasury (one percent of its budget) because of the yearly spending limits. The ability to carry over funding into the next fiscal year would permit more efficient management of grant dollars. We understand that this mechanism was recommended to the Committee and are disappointed to see that it was not included in this draft.

The major constraint on research progress is inadequate funding, yet the bill does not address this critical problem. Sustained and predictable funding is critical to maintain a highly productive research enterprise. However, since FY 2003, NIH has lost more than 23 percent of its capacity to support research due to a combination of budget cuts and inflationary losses. These losses have reduced the number of grants available and prematurely terminated many promising research projects and careers. While the goals of this draft bill are well intentioned, sufficient fiscal support is indispensable to fully realize them.

### **Many provisions legislate activities already underway, would micromanage NIH, and could interfere with decision making based on scientific merit**

The draft bill is overly prescriptive regarding how its goals should be accomplished. While some of the bill's provisions may lead to short-term benefits, the highly specific bill language will limit severely the

ability of federal agencies to adapt to future research challenges. Similarly, oversimplification of some issues within the bill will increase the likelihood of inadequate and inefficient solutions.

Careful planning and management of the NIH budget is important. However, Section 4001 of the draft bill mandates the creation of an NIH-wide strategic investment plan that defines extremely narrow parameters to determine funding priorities. Legislatively establishing a set of priorities will hinder progress by constraining inquiry. It will politicize the search for cures and create a never ending competition for targeted funding, limiting the discretion and judgment of the scientific leadership at NIH. This provision is duplicative with existing practices as all NIH institutes and centers (I/Cs) already develop strategic plans. Furthermore, it is unlikely that establishing 10 trans-NIH “strategic focus areas” as proposed in the bill, would enhance research planning within individual I/Cs. Currently each I/C establishes its strategic plan based on its specific mission and scientific opportunity, and this is superior to using a general list of “focus areas.”

Declining research funding, the limited number of faculty positions, and the increasing length of training all contribute to the instability of the biomedical workforce and the rising median age at which investigators receive their first major research grant. In sections 2261 and 2262, however, these issues are reduced to problems associated with how grants are awarded. The proposed adjustments will not address systematic workforce challenges and will likely shift some of the pressure to other career stages. NIH has already established provisions to help early career scientists, and their grant success rates are similar to those of experienced scientists. Also, NIH has issued analyses of the workforce and early career scientists, rendering the additional report mandated in the bill redundant.

### **Some sections are contradictory or superfluous in scope**

Some sections within the draft bill appear to have been added in isolation, with no knowledge or regard for subsequent provisions. For example, Section 4005 requires the Comptroller General to submit to Congress an analysis of the use and impact of Common Fund monies. One page later, Section 4007 authorizes additional funding for the Common Fund, effective before the Comptroller General’s report is released. Other provisions address matters that are not critical issues. To increase accountability, the bill institutes four year term limits for NIH I/C Directors in Section 4004. Considering that I/C Directors can already be removed from their positions, and that the strategic plans they develop (Section 4001)—on which their performance is judged—are longer than the proposed terms, the utility of this provision is questionable. Similarly, legislating the type of statistics (e.g. Bayesian methods) the FDA must accept for the review and approval of new drugs and medical devices is not likely to impact the rate at which new cures reach the public. It is also redundant with existing FDA guidance issued in 2010 on the use of these statistical methods.

This is a large, complex bill covering many agencies and issues. Our comments focus on the area we know best, NIH funded research. We appreciate, however, that some provisions of the bill are helpful to physicians and their patients. Title, IV Subtitle S, Continuing Medical Education Sunshine

Exemption, for example, makes an important correction to the Sunshine Act by excluding peer-reviewed journals, journal reprints, journal supplements, and medical textbooks from the reporting requirement. This removes a barrier that limited physicians' access to a valuable source of scientific information.

FASEB appreciates the Energy and Commerce Committee's concern for the future of biomedical research, and we share your desire to ensure that the U.S. remains a world leader in biomedical research. We encourage the committee to streamline future versions of the legislation and to focus the next draft on the major impediments to research progress. Within the next few weeks, FASEB will submit additional comments offering specific language to improve the draft bill.

Sincerely,

A large black rectangular redaction box covering the signature area.

Joseph R. Haywood, PhD  
FASEB President

February 27, 2015

The Honorable Fred Upton  
The Honorable Diana DeGette  
Committee on Energy and Commerce  
2125 Rayburn House Office Building  
Washington, DC 20515

Via electronic submission: [cures@mail.house.gov](mailto:cures@mail.house.gov)

Dear Chairman Upton and Congresswoman DeGette:

GlaxoSmithKline (GSK) is pleased to provide our comments in response to the Energy and Commerce Committee's 21<sup>st</sup> Century Cures draft discussion document. As a science-led global biopharmaceutical company dedicated to improving the quality of human life by enabling people to do more, feel better and live longer, GSK applauds your efforts to enhance the regulatory framework in support of biomedical innovation in the United States. We look forward to continuing to working partnership with the Committee and Congress on this initiative, and are thankful for your leadership and dedication on this critical issue.

**Title I: Subtitle A - Patient Focused Drug Development**

• **Section 1001:**

- One of GSK's core business values is to "Focus on the Patient" with the intent of always doing what is right for patients by focusing unmet needs to improve their healthcare by discovering and developing new medicines and vaccines that are meaningful to patients.
- The proposals outlined in this section of the draft legislation provide an important opportunity to enhance patient input and could potentially advance the science of patient input into medical product development and regulatory decision-making.
- Biopharmaceutical companies have been key contributors to the study and development of meaningful patient experience data which has been used to support development and approval of new medicines. As currently written, the draft legislation does not include data generated by biopharmaceutical companies in the definition of patient experience data and we suggest that the proposal could be significantly improved by including such data.
- We also note that the draft legislation requires workshop attendees to include patients, representatives from patient advocacy organizations and disease research foundations, representatives from the FDA review divisions, and methodological experts. It should be revised to also include representatives from biopharmaceutical companies, because such companies will be directly involved in collecting and applying patient-experience data in designing and implementing new clinical trials for innovative medicines.
- We would like to highlight that there are many examples of industry involvement with other key stakeholders resulting in the successful development of approaches to incorporate the patient perspective into drug development. For example, we would cite GSK's involvement with the Parent Project on Muscular Dystrophy to develop the first ever patient advocacy initiated draft FDA guidance on Duchenne muscular dystrophy. Also, industry involvement in the Critical Path Institute's PRO Consortium is an example of its participation in developing patient reported outcomes measures that are being developed with patient input and the highest standards in measurement science.



- Finally, we suggest that the draft legislation could be strengthened by suggesting a clearer linkage of patient experience data to inform drug development and regulatory decision-making. For example, decisions on clinical study designs, development and selection of clinical endpoints including PROs, benefit/risk assessments, and for understanding and removing barriers to patient participation in the clinical trials.

#### **Title I: Subtitle B - Surrogate Endpoint Qualification and Utilization**

- **Sections 1021 – 1024:**
  - Greater use of innovative drug development tools , such as biomarkers, surrogate endpoints, and patient reported outcomes (PROs), will bring significant efficiencies to drug development and will accelerate delivery of promising new medicines to patients. It is important that FDA continues to play a central role in the qualification and acceptance of such tools.
  - The provisions described in this section have the potential to improve the transparency and efficiency of the regulatory processes for qualification of new drug development tools. We support the language specifying time bound milestones for the overall qualification process to enhance the predictability of the process.
  - As currently written, the draft legislation is limited to the qualification of surrogate endpoints that are biomarkers. We feel the scope of this section should be broadened to include qualification of all biomarkers, surrogate endpoints as well as PROs to be used for drug development.
  - GSK supports that participation in the drug development tool qualification process is considered voluntary for requestors and that decisions about confidentiality and public disclosure will be determined by the requestor.
  - Finally, GSK feels there is a strong linkage between the provisions of this section with those described in Title I/Subtitle A regarding Patient Focused Drug Development. Greater involvement of patient perspectives in the drug development process can contribute to the identification and qualification of clinically meaningful endpoints for use in the clinical development of new medicines.

#### **Title I: Subtitle C - Approval of Breakthrough Therapies**

- **Section 1041:**
  - This section of the draft legislation provides FDA with an approval pathway that is explicitly linked to Breakthrough Designated medicines and has the potential to accelerate the availability of new medicines for treating serious or life threatening conditions of patients.
  - We support giving FDA increased flexibility by enabling the possibility to approve Breakthrough Designated medicines on the basis of early stage safety and effectiveness data which could include data from one or more phase 2 studies. The draft language should be amended to make clear that supporting evidence for this approval pathway is not limited to this type of data but could include other data considered appropriate by FDA.
  - The draft legislation gives FDA the authority to require the sponsor of a medicine approved under this pathway to study the safety and efficacy during the post marketing period. GSK supports the language that allows the possibility for such a requirement to be fulfilled using data sources other than randomized clinical trials, including from observational studies and registries.

### **Title I: Subtitle G – Expanded Access**

- **Section 1121 – 1125:**
  - GSK supports voluntarily posting general Expanded Access policies, where a program exists, in order to increase transparency and awareness for physicians and patients, rather than a statutory mandate linking them to regulatory designations, as outline in Section 1121.

### **Title I: Subtitle H – Facilitating Responsible Communication of Scientific and Medical Developments**

- **Section 1141 – 1161:**
  - GSK believes that proactive communication of healthcare economic information, comparative effectiveness research and real world evidence by healthcare stakeholders, including the biopharmaceutical industry can significantly benefit public health by providing population health decision makers with an expanded evidentiary base to match the right treatment with the right patient. However, regulatory guidance is needed to define uniform methodology standards for comparative effectiveness and real world research that can be appropriately shared.
  - The biopharmaceutical industry generates a significant amount of high-quality data that adheres to well-accepted research standards. Through the medicine discovery and development process, the biopharmaceutical industry acquires deep expertise that can provide a greater understanding of a disease, its treatment patters and affect on patients, as well as product performance, to meaningfully contribute to population health decision making.
  - Other healthcare stakeholders may freely and proactively communicate research findings, whereas, currently, the biopharmaceutical industry may only respond reactively to unsolicited requests on new use or “off-label” information via medical personnel. The FDA’s traditional view of permissible mechanisms for scientific exchange, such as responding to unsolicited questions and publishing scientific literature, does not foster timely communication of research findings.

### **Title I: Subtitle L - Dormant Therapies**

- **Section 1221 – 1223:**
  - GSK is supportive of this provision, aimed at encouraging the development of medicines to meet significant unmet medical needs

### **Title II: Subtitle C – Regenerative Medicine**

- **Section 2041:**
  - Regenerative medicine therapies offer new and transformational approaches to treat patients. GSK is supportive of efforts to provide regulatory guidance’s on the use of surrogate endpoints for accelerated approval of regenerative medicines.

### **Title II: Subtitle D – Genetically Targeted Platform Technologies for Rare Diseases**

- **Section 2051:**
  - GSK is supportive of this provision and would suggest the Committee consider the comments submitted by BIO and PhRMA.

## **Title II: Subtitle E- Sensible Oversight for Technology which Advances Regulatory Efficiency (SOFTWARE)**

- **Section 2061 – 2063:**

- Use of digital applications for continuous remote measurement of patients to better understand disease states and their response to treatment in a real world setting and in real time has the potential to transform and accelerate the way our industry discovers, develops, and delivers new medicines and cures for patients. GSK commends the Committee's efforts to develop guidelines and distinctions between software that should be regulated by the FDA (medical) and software that requires less oversight (health), though we believe the delineation between the two is not entirely clear. Like PhRMA, GSK supports the concept that clinical decision support (CDS) tools need not be regulated by the FDA like medical software, but would recommend the Committee consider other appropriate oversights for CDS to ensure it is derived from clinical practice, based on clinical evidence, and customized for an individual patient.

## **Title II: Subtitle F- Building a 21st Century Data Sharing Framework**

Building and supporting systems that link critical datasets is an important step towards accelerating 21<sup>st</sup> Century therapies for patients by enabling researchers to conduct diverse and stratified analyses, resulting in improved understanding of disease, advances in clinical research, and optimized delivery of novel treatments. GSK commends the Committee for taking actions to further advance the US learning healthcare system within this section. GSK supports the comments, from both BIO and PhRMA, sent to the Committee for consideration, and would like to add below:

- **Section 2081:**

- GSK supports the overall goal of making the CT registry as user friendly as possible. As well, it would be helpful to articulate if this is to be part of CT.gov or a separate data sharing clinical trial registry and if development of the data bank will be with consultation with stakeholders.

- **Section 2082:**

- Data should be both de-identified and anonymized (to ensure patient privacy and harmonization with what the term de-identification means in some European countries (where de-identification requires the additional step of anonymization in order to be label "de-identified").
- Real advancement in data sharing would be a provision to cover all trials submitted to CT.gov. In other words, a system should be established to provide access to data from both NIH studies and industry studies).
- Clarity is needed as to whether the established clinical trial data sharing entity would conduct analysis (solely or in conjunction with outside researchers) and to which the dissemination of results would apply.
- Data should be made available in a secured password protected environment ("controlled access") to balance significant concerns related to patient privacy and confidentiality as well as the need for valid scientific research using generally accepted scientific standard. The proposed access mechanism, however, appears to focused on 'registered users' and 'controlled contractual terms' and requires the entity to have "a plan in place to allow registered users to access and use de-identified clinical trial data, gathered from qualified clinical trials, available under carefully controlled contractual terms" as opposed to controlled access system. GSK believes the proposed mechanisms are not sufficient to balance the identified concerns.

- **Section 2085:**
  - GSK also suggests the Committee consider provisions for access to both Sentinel System and PCORNet, by industry and others.
- **Section 2091:**
  - GSK suggests the composition of the commission to include patient groups.
  - GSK suggests Qualified Clinical Data Registry Reporting (per CMS) – QCDR for the definition of the clinical data registry.

## **Title II: Subtitle G: Utilizing Real-World Evidence**

- **Section 2101:**
  - Many healthcare and research organizations generate and use evidence beyond what is typically required for product approval, including real world evidence. As the growing electronic data infrastructure improves access to data, policymakers and healthcare purchasers continue to explore ways to achieve high-value, high-quality healthcare to inform population health decision making. GSK believes that the use of real-world evidence can help to fill an “evidence gap” by providing decision makers with more comprehensive information to supplement Randomized Clinical Trial data to determine which treatment options are best for patients and ensure access to innovative, high-quality care.

## **Title II: Subtitle L - NIH Federal Data Sharing**

- **Section 2201:**
  - GSK is supportive of the sharing of data generated through research from federally supported grants, with the public.
    - GSK agrees with PhRMA that more clarity is needed around what “data” must be shared and the concerns around keeping confidential commercial information private.
    - Sharing of any anonymized individual level patient data would need to be done through a controlled access system to ensure patient privacy and use of data for valid scientific research.

## **Title II: Subtitle M - Accessing, Sharing, and Using Health Data for Research Purposes**

- **Section 2221:**
  - Access to high-quality healthcare and research data, ensuring patient privacy and confidentiality and legitimate scientific enquiry, with coordinated application of new technologies could ultimately lead to higher quality and greater value of healthcare systems and services, as well as speed the development of new therapeutic drugs. GSK is supportive of these provisions and would like to emphasize the importance of section 13444 as a key enabler of industry’s ability to collect a deeper understanding of disease states, treatment pathways, and improved patient outcomes.
- **Section 13444:**
  - More clarity is needed around if an individual withdraws their ‘authorisation’ of the data already collected. Can the data continue to be used for *ongoing* research that is aligned with the original authorisation or no further use at all?
- **Section 13445:**
  - GSK supports the principle that there needs to be independent review before (limited) personal information is used where prior authorization by the subject has not been obtained.

- **Section 13445:**
  - GSK suggests the Committee consider the ONC common clinical data set for the “limited data set” definition.

## **Title II: Subtitle N - 21st Century Chronic Disease Initiative Act**

- **Section 2241:**
  - Research and treatment of chronic diseases could benefit tremendously from the data rich environment of this proposed cohort study, especially in difficult to treat conditions such as Alzheimer’s disease (AD). AD, in its current state of understanding, will require decades of research to identify biomarkers and clinically relevant endpoints, lengthy clinical trials, and extensive target validation research to determine the most appropriate biological targets. A large coordinated effort is needed. GSK commends the Committee for proposing this patient cohort initiative to further the research environment for AD and potentially other diseases, including cancer as outlined and proposed in the President’s Precision Medicine Initiative. GSK suggests the Committee look for synergies between these two proposed efforts.

## **Title III: Subtitle B - Broader Application of Adaptive Designs and Bayesian Methods**

- **Section 3021:**
  - GSK believes that greater acceptance of adaptive clinical trial designs and Bayesian methods can help to accelerate the development and approval of new medicines while continuing to ensure that safety and effectiveness decisions are based on the most current and rigorous scientific standards.

## **Title IV: Subtitle C - Vaccine Access, Certainty, and Innovation**

- **Section 4041:**
  - GSK supports striking Section 4041: “Prompt review of vaccines by the Advisory Committee on Immunization Practices (ACIP).” While GSK recognizes that changes to the ACIP process could expedite decision-making, we believe that the specific changes needed are best determined by an evaluation of ACIP’s recent performance. Utilizing the evaluation to develop recommendations will help to ensure that any changes will achieve the desired result.
- **Additional Proposal to Consider in Title IV, Subtitle C**
  - GAO Study and Report on the Impact of Medicare and Medicaid Reimbursement Levels on Access to Vaccines  
GSK aligns with BIO in encouraging the Committee to consider a Government Accountability Organization (GAO) study on the impact of Medicare and Medicaid reimbursement levels on access to vaccines, especially for adults and the elderly, as well as all populations located in rural and underserved communities. The GAO should examine whether current levels of reimbursement or exclusion of vaccines from specific programs affects their use by physicians or access for beneficiaries. This report will help assess the amount to which reimbursement levels for providers and complex payment systems such as Medicare Part B and D impact access to vaccines for many Americans.

**Title V: Subtitle B - 21st Century Manufacturing**

- **Section 5021:**

- GSK has made a commitment to harnessing innovative technologies with the potential to transform both the way our medicines are made and our company's supply chain. We support establishing regulatory clarity in this 21<sup>st</sup> manufacturing environment and suggest language below:
  - Would require FDA to update its guidance regarding novel manufacturing techniques, to assure establishing an enabling regulatory environment to facilitate development and implementation of innovative pharmaceutical manufacturing approaches

December 10, 2014

The Honorable Tom Harkin  
Chairman  
Committee on Health, Education, Labor and Pensions  
428 Senate Dirksen Office Building  
Washington, DC 20510

The Honorable Lamar Alexander  
Ranking Member  
Committee on Health, Education, Labor and Pensions  
428 Senate Dirksen Office Building  
Washington, DC 20510

The Honorable Fred Upton  
Chairman  
Committee on Energy and Commerce  
2125 Rayburn House Office Building  
Washington, DC 20515

The Honorable Henry Waxman  
Ranking Member  
Committee on Energy and Commerce  
2322A Rayburn House Office Building  
Washington, DC 20515

**Re: Maintaining Patient Access to Compounded and Repackaged Medications**

Dear Chairman Harkin, Chairman Upton, Ranking Member Alexander, and Ranking Member Waxman,

Our organizations represent physicians, pharmacists, other healthcare providers, surgical centers, and patient advocates treating and providing care to patients with an array of conditions requiring a broad spectrum of treatments and also pharmacists that provide physicians, hospitals, and other health care professionals with compounded medications for administration to and treatment of patients within these practice settings (often called “office-use”). As such, we have been closely monitoring the Food and Drug Administration’s (FDA) implementation of the *Drug Quality and Security Act* (“DQSA”, P.L. 113-54) and remain concerned about the impact of the Agency’s actions on patient access to compounded medications.

We are deeply concerned about the implementation of the DQSA in regards to both compounded and repackaged medications for office-use. The most recent implementation actions of the FDA have resulted in decreased patient access to vital medications and have caused confusion amongst state boards of pharmacy, health care providers, pharmacists, and patients.

Many medical professionals rely on various types of repackaged and compounded medications to treat their patients -- whether it is in their office, on a crash cart in an emergency department, or in another medical setting. These medications are essential for emergency situations as well as to start treatment immediately in response to a medical condition. Medications, including some biologics, are compounded or repackaged in order to meet specific dosage needs and are critical to the timely treatment of many patients when a prescriber determines that a FDA-approved drug product is neither available nor appropriate to treat their condition.

Over the past year, access has declined for both repackaged and compounded medications, particularly those ordered without a patient-specific prescription and administered within a healthcare setting for “office-use.” Some examples of such care barriers include:

- Antibiotics for urgent and emergent use in treating ophthalmology patients;
- Buffered lidocaine for use in dermatology procedures;
- Vascular endothelial growth factor inhibitors used in treating age-related macular degeneration by ophthalmologists;
- Injection therapies used to treat erectile dysfunction in urology patients. Test injections are commonly administered in the doctor’s office to determine correct dosage;
- Cantharidin to treat viral skin conditions in office by dermatologists and pediatricians;
- Injectable methylcobalamin for the treatment of pernicious anemia and other vitamin B-12 deficiencies.

Maintaining access to essential repackaged and compounded medications for office-use is not only vital for patients, but is consistent with the legislative intent of the DQSA.<sup>1,2</sup> While reinforcing Section 503A of the *Food, Drug and Cosmetic Act* (FDCA) through the passage of the DQSA, Congress came together in a bipartisan and bicameral fashion to make clear that pharmacists’ ability to provide compounded medications for a prescriber’s administration to or treatment of a patient within their practice should be left to the states -- office-use of compounded medications is currently regulated under state law.<sup>3</sup>

As with office-use, the DQSA did nothing to limit repackaging, and Congressional intent was that FDA would continue to allow the practice of repackaging of medications.<sup>4</sup> Actions by FDA to limit access to repackaged medications, either by requiring a patient-specific prescription in all cases or by not allowing pharmacists to engage in repackaging, would have significant consequences for patients who rely on these

---

<sup>1</sup> Senator Isakson (GA), Senator Alexander (TN), and Senator Boozman (AR). “Drug Quality and Security Act.” *Congressional Record* 159: 164 (November 18, 2013) p.S8071. Available from Thomas.gov; Accessed 11/24/2014.

<sup>2</sup> Representative Griffith (VA), Representative Burgess (TX), and Representative Green (TX). “Drug Quality and Security Act.” *Congressional Record* p.H5963. Available from: Thomas.gov; Accessed 11/24/2014.

<sup>3</sup> Senator Isakson (GA), Senator Alexander (TN), and Senator Boozman (AR). “Drug Quality and Security Act.” *Congressional Record* 159: 164 (November 18, 2013) p.S8071. Available from Thomas.gov; Accessed 11/24/2014.

<sup>4</sup> Senator Harkin (IA), Senator Alexander (TN), and Senator Boozman (AR). “Drug Quality and Security Act.” *Congressional Record* 159: 164 (November 18, 2013) p.S8072. Available from Thomas.gov; Accessed 11/24/2014.



therapies.<sup>5</sup> As the DQSA did not explicitly provide for repackaging by either 503A pharmacies or the newly-created 503B outsourcing facilities, physicians and patients are now forced to rely on the FDA for issuance of further guidance on this issue.

Congress' multiple statements in the *Senate Congressional Record* show clear and overwhelming intent that compounded preparations for office-use remain available after the passage of the DQSA. These numerous statements as well as strong urging from physician and pharmacy stakeholders, did not direct the agency to limit office-use medication preparation by 503A compounders. In addition, when FDA considered changes to the Compliance Policy Guide (CPG) for human compounding several years ago, the draft CPG specifically provided for office-use.<sup>6</sup> Despite these statements and its own draft guidance, FDA stated in a September 15, 2014 response to a bipartisan letter from Congress that to comply with 503A, a compounding pharmacist may not dispense compounded medications for office-use, but rather, must obtain a prescription for an individually identified patient.<sup>7</sup>

Unfortunately, FDA's position interferes with the practice of medicine and decreases patient access to medications. In many situations, a provider must be able to have a compounded drug on hand in order to treat patients presenting with urgent or emergent conditions for which treatment delays may be extremely detrimental. In order to preserve patient access to medications, we ask that Congress address the concerns with office-use and repackaged compounded medications legislatively as soon as possible so that providers and patients can have access to these essential treatments and/or work with FDA on a responsible regulatory approach.

Sincerely Yours,

Alliance for Natural Health USA (ANH-USA)

Alliance of Independent Pharmacists of Texas (AIP)

---

<sup>5</sup> Senator Isakson (GA), Senator Alexander (TN), Senator Harkin (IA), Senator Warner (VA), Senator Burr (NC), and Senator Boozman (AR). "Drug Quality and Security Act." *Congressional Record* 159: 164 (November 18, 2013) p.S8071. Available from Thomas.gov; Accessed 11/24/2014.

<sup>6</sup>United States. Department of Health and Human Services. Food and Drug Administration. *Pharmacy Compounding of Human Drug Products Under 503A of the Federal Food, Drug, and Cosmetic Act Draft Guidance*. Washington, DC: n.p., 2013. Print.

<sup>7</sup> United States. Department of Health and Human Services. Food and Drug Administration. *Response to Congressional Letter on Office Use*. September 15, 2014.

Ambulatory Surgery Center Association (ASCA)  
American Academy of Dermatology Association (AADA)  
American Academy of Environmental Medicine (AAEM)  
American Academy of Ophthalmology (AAO)  
American Association of Naturopathic Physicians (AANP)  
American College for Advancement in Medicine (ACAM)  
American Medical Association (AMA)  
American Pharmacists Association (APhA)  
American Society of Cataract and Refractive Surgery (ASCRS)  
American Society of Consultant Pharmacists (ASCP)  
American Society of Retina Specialists (ASRS)  
International Academy of Compounding Pharmacists (IACP)  
International College of Integrative Medicine (ICIM)  
International Hyperbaric Medical Association (IHMA)  
International Organization of Integrative Cancer Physicians (IOIP)  
National Alliance of State Pharmacy Associations (NASPA)  
National Community Pharmacists Association (NCPA)  
PCCA  
The Integrative Medicine Consortium (IMC)  
The Macula Society



To: The Honorable Fred Upton, Chairman, House Energy & Commerce Committee  
From: JDRF  
Date: February 24, 2015  
Re: 21st Century Cures Discussion Draft

On behalf of JDRF and the many individuals and families JDRF represents who are personally affected by type 1 diabetes (T1D), thank you. JDRF greatly appreciates you and your colleagues on the Energy and Commerce Committee for working to address barriers that are hindering innovation and the discovery, development, and delivery of new therapies to patients. As you know, JDRF, formerly known as the Juvenile Diabetes Research Foundation, is the leading global organization funding T1D research, with a goal of progressively removing the impact of T1D from people's lives until we achieve a world without T1D. JDRF appreciates the opportunity to provide the following comments regarding the 21<sup>st</sup> Century Cures Initiative Discussion Draft and looks forward to working with you and your team to advance this effort this year.

#### **TITLE I - PUTTING PATIENTS FIRST BY INCORPORATING THEIR PERSPECTIVES INTO THE REGULATORY PROCESS ADDRESSING UNMET NEEDS**

##### ***Section 1001 - Patient Experience Data***

JDRF is pleased that the Discussion Draft encourages the inclusion of patient experience data in a structured risk-benefit assessment framework for drugs. We think that by focusing on patients the regulatory process will be strengthened and medical product development will be improved. This is especially important for a disease like type 1 diabetes that is largely self-managed. To strengthen this provision, we suggest that the structured risk-benefit assessment framework be required to include patient experience data or justify why it is not necessary to ensure that those factors that are meaningful to patients are considered as a therapy is developed. Furthermore, we suggest that a similar requirement be made of the medical device approval process for class III and innovative class II devices. This would supplement the ongoing efforts by the Center for Devices and Radiological Health to incorporate patients into the regulatory process using their benefit-risk framework and the Patient Preferences Initiative.

##### ***Sections 1021 & 1022 - Surrogate Endpoint Qualification***

JDRF is supportive of the provisions in the Discussion Draft that would establish a process with defined timelines for qualification of surrogate endpoints. Since surrogate endpoints demand the most evidence to be qualified, a more defined regulatory focus on this type of tool with the development of a guidance document will foster development and allow us to realize the benefit of new medical therapies in a

shorter time. A requirement to develop disease specific guidance for evidentiary requirements for surrogate endpoint would further encourage research and development of new markers. We are pleased that the evidentiary requirements and process will apply to all product types, drugs, medical devices, and biologics so that there is a consistent process. We would suggest that, to further foster development and use of surrogate endpoints and other biomarkers and to better support the external qualification of biomarkers authorized in this section, the Agency be required to establish an Agency-wide office to support biomarker development/qualification instead of the existing center-specific programs.

#### ***Section 1041 - Approval of Breakthrough Therapies***

JDRF is supportive of this provision that allows approval of certain drugs after phase 2 studies.

#### ***Section 1081 & 1101 – Breakthrough Devices***

It is important to JDRF that similar regulatory opportunities be available for drugs, medical devices, and biologics and we are therefore pleased that the Discussion Draft includes a Breakthrough pathway for medical devices. For this pathway to be impactful, it needs to be transparent and provide tangible benefits in terms of review and approval. The requirements for the priority review in the discussion draft are not very concrete or specific and there are no timelines associated with them. We recommend that the provisions provide the Agency with specific timelines and other expectations regarding accelerating approvals of breakthrough technology. In addition, we support the various possible criteria for the pathway, including that no approved alternatives exist or the therapy offers significant advantages over existing approved or cleared alternatives or has the ability to reduce the need for hospitalization, improve quality of life, or facilitate patients' ability to manage their own care. We also note that the final possible criteria for this pathway ("in the best interest of patients") could be interpreted to include most new devices and suggest amending it. While we are in favor of the maximum number of devices and therefore patients benefitting from a breakthrough device program, if too many devices are made eligible, the resources of the program may be diluted, undermining the intention of the program.

#### ***Section 1181 – Streamlined Data Review Program***

The provisions establishing a Streamlined Data Review Program could provide a valuable opportunity to encourage "repurposing" or new uses for existing drugs which could accelerate new therapies addressing unmet needs. However, the provision as currently written is too narrow, and JDRF strongly encourages Congress to expand the definition of "qualified indication" in this section to include not only cancer, also autoimmune and chronic diseases such as diabetes. JDRF believes there is great potential for accelerating therapies for type 1 diabetes by repurposing drugs already utilized for other indications, and would strongly encourage the Committee to expand this provision.

#### ***Section 1202 – Repurposing drugs***

JDRF supports the authorization of additional funds for the National Center for Advancing Translational Science (NCATS) to conduct research on repurposing drugs for new uses. As noted above, JDRF believes there is great potential for accelerating therapies for type 1 diabetes by repurposing drugs already

utilized for other indications. This provision would apply particularly to drugs and biological products where patents and exclusivity periods have expired. There is a current example of how NIH funds are being used for such a purpose in an area important to JDRF. Currently, the Special Diabetes Program is funding a clinical trial using allopurinol, a generic drug used to treat gout that has promise for preventing kidney failure among those with T1D. Without this funding, the trial would not have begun due to the lack of a commercial incentive to test this compound for this purpose. Should this trial show that allopurinol is effective in mitigating the loss of kidney function in patients with T1D, a tangible treatment for people with T1D could follow in the study's footsteps. We believe that with additional funding, NCATS will be able to address similar areas of unmet need where commercial incentives are minimal.

In addition, the Committee might consider whether additional incentives involving patents and exclusivity periods might help provide additional incentives for repurposing of drugs. We realize this is a complex area, but would recommend additional consideration of it as the 21<sup>st</sup> century cures initiative moves forward.

## **TITLE II – BUILDING THE FOUNDATION FOR 21<sup>ST</sup> CENTURY MEDICINE, INCLUDING HELPING YOUNG SCIENTISTS**

### ***Section 2001 – Innovative Cures Consortium***

JDRF is as strong supporter of public-private partnerships and routinely collaborates with leaders in government, academia, health care, and industry to advance its mission. As such, JDRF supports the inclusion of patient representatives as part of the Board of Directors, should the Consortium be created. Additionally, JDRF respectfully requests that the Consortium defines opportunities for additional patient input and receives appropriate funding to carry out its mission.

### ***Section 2201 –Accessing, sharing, and using health data for research purposes***

JDRF supports efforts to promote data sharing for those receiving NIH grants provided that patient confidentiality is maintained, as noted in the draft language.

### ***Section 2241 – Plan for longitudinal study of outcomes of patients with a chronic disease***

JDRF applauds the committee for its focus on the need for longitudinal studies on outcomes with patients with chronic diseases. In the area of type 1 diabetes (T1D), the Committee's support for the Special Diabetes Program has enabled the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to carry out critical longitudinal T1D studies, including the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications trial (DCCT/EDIC), The Environmental Determinants of Diabetes in Youth (TEDDY), and The Search for Diabetes in Youth Study (SEARCH).

Given the current work already underway by NIDDK, continued funding of the Special Diabetes Program is the best mechanism for longitudinal studies of outcomes of patients with T1D. However, we

recognize that the mechanism proposed by the language in this section might be useful for other chronic diseases.

***Section 2261 – Funding research by emerging scientists through the Common Fund***

JDRF supports efforts to provide additional funding to emerging scientists and appreciates the language that notes additional funds “shall be used to supplement, not supplant, the funds otherwise allocated by the National Institutes of Health for young investigators”.

**OVERALL COMMENT ON NIH FUNDING**

In addition to the comments noted above, JDRF encourages you and your Committee colleagues to continue your strong support for resources for the National Institutes of Health by incorporating proposals for increased funds for biomedical research into the 21<sup>st</sup> Century Cures Initiative, as well as renewing the Special Diabetes Program which is critical for type 1 diabetes research.

**CONCLUSION**

Thank you again for the opportunity to contribute to this comprehensive and innovative effort. Please do not hesitate to contact Laura Whitton, JDRF’s Senior Director, Government Relations & Advocacy at [REDACTED] regarding next steps in this important effort.



March 12, 2015

The Honorable Fred Upton, Chairman  
Energy and Commerce Committee  
U.S. House of Representatives  
Washington, D.C. 20515

The Honorable Diana DeGette  
Energy and Commerce Committee  
U.S. House of Representatives  
Washington, D.C. 20515

Dear Chairman Upton and Rep. DeGette:

On behalf of National Brain Tumor Society (NBTS), the largest nonprofit organization in the United States dedicated to the brain tumor community, we write to commend your leadership of the 21<sup>st</sup> Century Cures Initiative. The Initiative and your staff have facilitated an open process and have set a high standard for inviting and involving participation from the patient advocacy community. We appreciate your inclusive style. We also write to respectfully offer reaction and recommendation to the discussion draft released in January 2015. Our comments and recommendations are discussed below by section.

As background, brain tumors comprise a group of over 120 diseases, and tragically can impact the lives of people at any age, of either gender, and of any race or ethnic origin. Brain tumors are now the leading cause of cancer death in children under 10. It is one of the so-called deadliest cancers because it has a five year survival rate of less than 50%, and for glioblastoma, the most common malignant form of brain tumor, the survival rate is a dismal 4.7% five year survival rate. There is no cure, and there are very few, if any treatments that extend survival by more than a few months. While some brain tumors may be considered benign, they are all potentially life-threatening. While progress is being made, and a more in depth understanding of the nature of brain tumors is evolving, far more investment in research is needed to advance toward a cure. This research must be coupled with a reduction of the barriers inherent in the drug development process for orphan drugs, to incentivize the major stakeholders to increase investments in the brain tumor arena.

The 21<sup>st</sup> Century Cures Initiative Discussion Draft offers many ideas that could stimulate and propel drug development forward. What follows are the NBTS comments about select sections of the discussion document, followed by recommendations for new provisions we hope you will consider incorporating into future versions of this legislation.

Title I, Subtitle A – Patient Focused Drug Development

#### DEVELOPMENT AND USE OF PATIENT EXPERIENCE DATA TO ENHANCE STRUCTURED RISK-BENEFIT ASSESSMENT FRAMEWORK

National Brain Tumor Society supports the concept of a structured risk-benefit framework in the drug development process. We believe that this will provide a means of including patient experience in the drug development process, which would give primacy to patients and their particular disease, unlike a treatment-centric process.

**NBTS Recommendation:** We recommend that the framework start with a clear understanding and definition of what “risk” means to patients and families. For example, the concept of risk in a clinical trial may be different for a glioblastoma patient with a rapidly progressing, deadly disease than for a patient with a different form of cancer with a less aggressive course of malignancy. We also urge that this section highlight the particular value and necessity of parent input into the risk-benefit assessment during the development of pediatric drugs, including those developed for childhood brain tumor patients. We believe that caregiver input can be just as vital to the development of patient experience as patients, and this notion should be included in this section.

We support the idea of permitting outside groups, including patient advocacy organizations, to submit patient experience data in a standardized manner to enhance structured risk-benefit frameworks. Advocacy groups are increasingly taking on the burden of collecting patient data, including data tracing the natural history of the disease and we encourage the establishment of registries that can provide natural history data of brain tumors. Such information is valuable for research, selection of treatments and prognostication. As cancer and other diseases are increasingly subdivided into molecularly and symptomatically distinct groups, external support from advocacy organizations will be critical in providing large amounts of information from a broad sampling of the population that they represent. Such data may not be available with the same level of detail should one seek simply a random sample of patients with a broad diagnosis. Finally, we encourage this section to build upon and help improve the patient-focused drug development initiative that was enacted as part of the 2012 Food and Drug Administration Safety and Innovation Act. The Food and Drug Administration (“FDA”) has taken great strides in the establishment of this initiative, and it would be senseless to duplicate the steps that have already been taken, taking more time from patients than they have to give.

#### Subtitle B—Surrogate Endpoint Qualification and Utilization

#### SEC. 507. EVIDENTIARY STANDARDS FOR THE REVIEW OF REQUESTS FOR THE QUALIFICATION OF SURROGATE ENDPOINTS

Surrogate endpoints are critical in the drug development process and eventual approval of many therapies, including brain tumor treatments. Establishing the validity of surrogate endpoints is an essential requirement for their incorporation into a clinical trial to evaluate a drug, particularly for those therapies that intend to gain approval through the accelerated approval regulatory pathway. The FDA Office of Hematology and Oncology Products has shown openness the use of various types of surrogate endpoints in clinical trials, including time to progression and time to event endpoints as well as progression free survival. National Brain Tumor Society supports the concept of creating criteria for the qualification of surrogate endpoints. Establishing a clear process for the development of surrogate endpoints would shorten the development time, and provide more certainty for drug sponsors regarding the acceptability of endpoints.

**NBTS Recommendation:** We urge the committee to require the development of criteria for qualification of surrogate endpoints, and request that these criteria provide for the use of retrospective data to support qualification. The ability to use retrospective data to support the establishment of an endpoint will help accelerate the process, and reduce the cost of having to



develop and complete a prospective clinical trial to for endpoint establishment, which can add years to endpoint qualification.

#### BIOMARKERS PARTNERSHIP

Biomarker validation is critical for brain tumor drug development, and NBTS encourages more prolific biomarker development, especially imaging-based biomarkers. But biomarkers are as numerous as the diseases for which they are developed, and it is often difficult for the scientists and pharmaceutical companies to prioritize biomarker development and qualification. To the extent that such public-private partnerships can facilitate the review of requests for biomarker qualification, it could benefit the process. That said, we urge that disease expertise is necessary in biomarker review. Therefore should other non-FDA partners be involved in brain tumor biomarker qualification we urge that there be a requirement that they have particular brain tumor expertise.

NBTS Recommendation: We recommend that this section include encouragement for the FDA to seek out partnerships with both the public and private sectors that facilitate the development of imaging-based biomarkers. Imaging-based biomarkers are of particular importance in the brain tumor field, and their development and validation is urgently required. If developed and implemented successfully, they could become a lynchpin for drug development, and enable future adaptive clinical trials, which will hopefully be as successful as the ISPY2 clinical trial.

#### Subtitle C—Approval of Breakthrough Therapies

National Brain Tumor Society supports the concept of breakthrough therapies, and views this program as a means of ultimately accelerating the development and approval of new drugs that are both safe and effective for brain tumor patients. By allowing the Sponsor of a new drug to meet safety data requirements in earlier phase trials, this provision, subject to the development of guidance, represents a step toward appropriate acceleration of approvals. Moreover, this provision provides the FDA greater authority to accelerate the approval process without compromising patient safety by requiring a post-marketing assessment plan. We support the requirement of patient input into the guidance document related to approval of breakthrough therapies.

#### Subtitle E—Priority Review for Breakthrough Devices

We support the concept of priority review for breakthrough devices. Like the provision for breakthrough therapies, this provision has the potential to accelerate development of new treatments for many different diseases and conditions, some of which may benefit more from a medical device-based treatment than through pharmacologic means

#### Subtitle F—Accelerated Approval for Breakthrough Devices

NBTS supports the concept of accelerated approval for breakthrough devices for the same reasons as priority review.

#### Subtitle G—Expanded Access

#### SEC. 1121. EXPANDED ACCESS POLICY AS CONDITION OF EXPEDITED APPROVAL

National Brain Tumor Society supports greater transparency from the pharmaceutical industry with regard to expanded access policies. The patient community as a whole, as well as the treating physicians, would benefit from a more clear understanding of industry policies on expanded access requests, including submission and review of the requests.

NBTS Recommendation: We recommend that the definition of “covered investigational drug” be expanded to include “drugs with a mechanism of action or purpose that may be applicable for the treatment of pediatric cancer.”

We also encourage the addition of a requirement that industry sponsors be limited to a two-week review period for expanded access requests in cases where the therapy is intended to treat a disease with a life expectancy of less than two years. Further, we believe that the process for making the request should be made available on the website of the industry sponsor as well as on a web-based list hosted by the FDA and NIH.

#### EXPANDED ACCESS TASK FORCE

National Brain Tumor Society supports the formation of the Task Force on expanded access as stated in the draft legislation.

NBTS Recommendation – We recommend that the task force specifically include a parent of a pediatric cancer patient as well as a caregiver or patient from a deadly or recalcitrant cancer (defined as a cancer with a less than 50 percent five year relative survival rate).

#### Subtitle N—Orphan Product Extensions Now

##### EXTENSION OF EXCLUSIVITY PERIODS FOR A DRUG APPROVED FOR A NEW INDICATION FOR A RARE DISEASE OR CONDITION

Many types of brain tumors may be considered rare diseases. Thus, NBTS encourages the use of appropriate market-based incentives for brain tumor drug development for both adult and pediatric patients. To the extent that increased market exclusivity will help incentivize sponsors to invest in pediatric cancer and/or rare diseases such as brain tumors, this provision could provide sponsors motivation to pursue new applications for drugs they previously received orphan drug status designation.

#### Subtitle M—Accessing, Sharing, and Using Health Data for Research Purposes

##### ALLOWING ONE-TIME AUTHORIZATION OF USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES.

The discussion draft would authorize the use or disclosure of protected health information (PHI) of the individual with respect to all future research purposes, including the use and disclosure of protected health information of the individual that is collected after the date of such authorization, and such one-time authorization shall satisfy the requirement under paragraph (1)(iv) of such section with respect to such future research if such authorization—  
*“(1) sufficiently explains that the information will be used and disclosed for future research; and (2) states that the authorization will remain valid unless and until it is withdrawn by the individual; and permits the individual, and provides instruction to the individual on how to opt-out of, or otherwise withdraw, such authorization at any time.”*

**NBTS Recommendation:** With respect to the section above, we recommend that the Committee include protection for the patient and/or their family by requiring the return of aggregate information to the patient and/or family following the completion of the research for which the PHI was collected.

Subtitle O—Helping Young Emerging Scientists

SEC. 2261. FUNDING RESEARCH BY EMERGING SCIENTISTS THROUGH COMMON FUND.

National Brain Tumor Society encourages funding of emerging scientists and supports this section. We agree that funding of young and emerging scientists through the Common Fund should supplement and not supplant existing funds supplied by the NIH.

NBTS Recommendation – We urge that language be added to this section that at least a portion of the funding be allocated to fund emerging scientists working in the areas of rare cancers, especially deadly cancers (defined as those with less than 50% five year survival rate and in both adults and children). The value of this recommendation is to create an economic incentive for emerging scientists who are struggling to become eligible for R program funding from the NIH.

Title II: Building The Foundation for 21<sup>st</sup> Century Medicine, Including Helping Young Scientists

Subtitle A - 21<sup>st</sup> Century Cures Consortium Act

Recommendation: National Brain Tumor Society recommends that this consortium seek out ways to hurdle barriers to drug development in pediatric oncology and rare disease in general. While many Americans face brain tumor and other rare disease diagnoses, the markets for drugs are relatively small. Congress and the FDA are to be commended for placing emphasis on rare disease including pediatric cancer in the FDASIA legislation of 2012 and enacting new market incentives for drug development. We encourage the Committee to ensure the new Consortium focus on the challenges of improving and developing incentives for industry to invest in the development of pediatric and rare disease treatments.

Subtitle D - Genetically Targeted Platform Technologies for Rare Diseases

Although brain tumors are predominantly characterized by alterations in multiple genes, which may render them less amenable to a single gene therapy approach, National Brain Tumor Society fully supports use of clinically proven genetically targeted platform technology to develop novel treatments strategies for patients.

Subtitle F - Building a 21<sup>st</sup> Century Data Sharing Framework

National Brain Tumor Society supports standardization of data for a clinical trial registry data bank. This is particularly important in the recruitment of small patient populations for clinical trials on rare diseases such as brain tumors. Educating the patient and family community about the opportunities that such a registry will provide will be important. We also support the sharing of de-identified data for the purposes of driving clinical research.

Subtitle G—Utilizing Real-World Evidence

NBTS supports the use of credible and quality assured real-world data on patient outcomes to support post-approval study requirements. The use of real-world data to support the use of a drug for a rare disease will be particularly important because such data may supplement data from the smaller numbers of patients involved in the randomized clinical trial setting and enable

earlier decisions to be made. It will be important to ensure that data sources are credible and representative of the heterogeneity of the disease and that patient outcome assessment is based on both quality of life metrics (including clinical outcome assessments) as well as overall survival statistics.

#### Subtitle L - NIH–Federal Data Sharing

NBTS supports the proposal to incorporate data sharing policy for NIH supported research. Rare diseases such as brain tumors are often complex and heterogeneous at the molecular level. Access to a multi-dimensional data platform that allows integration and analysis of datasets from scientific and clinical sources will help guide and inform innovative research for treatment development.

### Title III: Modernizing Clinical Trials

#### Subtitle B—Broader Application of Bayesian Statistics and Adaptive Trial Designs

We support the concept of standards for using adaptive trial designs and Bayesian methods in clinical trials. National Brain Tumor Society is actively exploring the application of adaptive clinical trial designs as part of drug development in brain tumors. Standards for using the adaptive trial designs should aim to bring consistency and reliability in these trials, in order to satisfy regulatory criteria. However, we recommend that latitude be given to construct and validate different types of adaptive trial designs, based on the study population.

#### Subtitle E—Global Pediatric Clinical Trial

We support the concept of a global network of young investigators to plan a clinical trial, as long as the project has sufficient oversight from a major National Cancer Institute designated cancer hospital, with significant experience in pediatric brain tumor clinical trials.

### TITLE IV—Accelerating the Discovery, Development and Delivery Cycle and Continuing 21<sup>st</sup> Century Innovation at NIH, FDA, CDC and CMS

#### Subtitle A—National Institutes of Health SEC. 4001. NIH RESEARCH STRATEGIC INVESTMENT PLAN

We support the concept of a strategic investment plan.

NBTS Recommendation: Development of the plan should include robust input from patient advocacy organizations across disease areas, including brain tumors. Strategic focus areas for consideration should prioritize recalcitrant cancers including those that have a less than 50% five-year relative survival rate, in addition to rare and pediatric cancers.

NIH Investment Plan continued:

SEC. 4008. ADDITIONAL FUNDING FOR NIH BRAIN RESEARCH.

Recommendation: National Brain Tumor Society supports the concept of funding for NIH brain related research and requests that this section specifically state that brain tumor research is considered to be among the types of brain-related research envisioned in this section, and would be eligible for NIH funding.

## **Recommendations for New Provisions To Be Added to the 21<sup>st</sup> Century Cures Legislation**

### Increase Investment in Cancer and Rare Disease Research Through the National Institutes of Health

National Brain Tumor Society urges the inclusion of a section of the 21<sup>st</sup> Century Cures legislation to call for both increasing funding for the National Institutes of Health, specifically the National Cancer Institute and National Institute for Neurological Disorders and Stroke. These two institutes provide the majority of funding for brain tumor research. We also urge the Committee to support the Accelerating Biomedical Research Act recently introduced by Rep. DeLauro. The legislation would help create a stable funding platform for the NCI and NIH overall. As the Committee knows, NIH funding has been unable to keep pace with inflation, and is not funded at a level adequate to leverage recent advancements in cancer research, including the results of The Cancer Genome Atlas. This recent advancement is leading researchers, including those in brain tumors research, toward the knowledge that will be critical in the discovery and production of targeted, “precision” medicines for patients.

### Leverage the Investment Made in The Cancer Genome Atlas

We urge the Committee to include a section in the legislation directing the National Institutes of Health to develop a specific line of grant funding dedicated to research projects designed to utilize the information collected by The Cancer Genome Atlas (TCGA). The TCGA project is coming to a close, but this project has been a terrific example of an effort to launch genomic research in cancer, and the data collected with propel it toward use in clinical research. When this project ends, there needs to be a new effort to ensure that the genomic information is being used for drug development. This is particularly important in the brain tumor field, a glioblastoma was the first tumor type sequenced by TCGA. As a result of this effort, we now know more about how subtypes of low-grade gliomas may evolve into glioblastomas, and thus might need the same or similar treatment strategies. We are at the cusp of realizing the value of TCGA for patients, and this is the time to secure Congress’ previous investment in this legacy.

### Biospecimen Acquisition Requisite to Precision Medicine

Quality assurance in the acquisition, analysis, and storage of biospecimens are essential for biomedical research and to the development of precision medicines. The 21<sup>st</sup> Century Cures Initiative can facilitate an effort to improve the process so that researchers have quality tissue to use in their research. We recommend that the 21<sup>st</sup> Century Cures legislation do the following:

1. Require adherence to the National Cancer Institute’s Best Practices for Biospecimen Resources by NIH funded institutions that collect biospecimens either for research or for the purpose of clinical treatment. We urge that the NIH be directed to provide funding to enable compliance.
2. Direct the Department of Health and Human Services to work with providers including but not limited to those at NCI designated cancer centers to determine reimbursement policies under Medicare and Medicaid to facilitate improved biospecimen collection, and procedures deemed necessary for precision medicine based treatment selection including pre-surgical planning/imaging, surgical and tissue collection/storage procedures to pathology.

3. Direct the Department of Health and Human Services to establish specific reimbursement at appropriate levels for laboratory diagnostic tests that are deemed essential for biospecimen collection and precision medicine approaches to the treatment of cancer
4. Direct the National Institutes of Health to increase investment in research designed to validate new imaging and molecular biomarkers particularly in cancer including those cancers such as brain tumors with less than a 50% five year relative survival rate.
5. Direct the Department of Health and Human Services to identify and improve reimbursement for medical techniques and technologies that both improve biospecimen acquisition.
6. Direct the Department of Health and Human Services to require that NIH funded institutions with collections of cancer biospecimens or biobanks report their collection on the NCI's specimen resource locator.

#### Facilitating Pediatric Oncology Research and Drug Development

We urge the Committee to include in the legislation language that would amend section 505B of the Food, Drug and Cosmetic Act, also cited as 21 U.S.C Section 355C – RESEARCH INTO PEDIATRIC USES FOR DRUGS AND BIOLOGICAL PRODUCTS by doing the following:

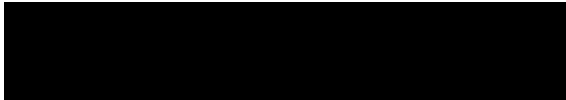
- remove the waiver under this section for orphan drugs and
- require that for an oncology drug, an assessment under Section 505B (a)(2) may be required for a pediatric oncologic indication if the molecular target or mechanism of action of the drug for an adult oncologic indication is highly relevant to any pediatric cancer(s).

These recommended changes would help ensure that assessments for pediatric oncology drugs are conducted when drug sponsors seek approval for adult oncologic drugs, preventing a delay of pediatric drug development.

National Brain Tumor Society appreciates the opportunity to comment on the 21<sup>st</sup> Century Cures Initiative Discussion draft. We commend you, Chairman Upton and Congresswoman DeGette, for your leadership in this effort to improve the research and development pathways, your commitment to remove the barriers inherent in the current drug development system.

We would be happy to meet with you and your staff to discuss your legislation and our recommendations.

Sincerely,



David F. Arons, JD  
Chief Public Policy and Advocacy Officer  
[darons@braintumor.org](mailto:darons@braintumor.org)  
617-393-2861



Working Together for an Affordable Future

March 3, 2015

The Honorable Fred Upton  
Chairman  
Committee on Energy and Commerce  
United States House of Representatives  
Washington, DC 20015

Dear Chairman Upton:

NCHC is a coalition of more than 80 member organizations—representing health care providers, purchasers, payers, and consumers—committed to promoting an affordable, high-quality health system in the United States. We are pleased to have the opportunity to comment on the 21<sup>st</sup> Century Cures Act Discussion Draft, released on January 27, 2015.

NCHC commends the Committee for its efforts to encourage innovation in pharmaceuticals and medical devices. New medical technologies and therapies have dramatically improved patients' prognoses and quality of life, and, in some cases, have even offered the possibility of a cure. Precision Medicine, in particular, promises significant breakthroughs in the treatment of a range of diseases, including cancer. Therefore, we are pleased that the discussion draft included an array of provisions to ensure a faster, more efficient path for new medical innovations. **NCHC supports in principle the Committee's efforts to promote surrogate endpoint qualification and utilization, an improved data sharing network, and broader application of adaptive trial designs.** When combined with adequate support for basic and translational research and careful attention to patient safety, these bipartisan proposals can help speed new treatments to the market.

However, the speedier introduction of treatments will mean nothing if patients and our health system cannot afford them. NCHC is gravely concerned that the discussion draft ignores the fundamental challenge of affordability.

In fact, some provisions of the discussion draft would sacrifice the affordability of prescription drugs in the name of promoting innovation. For example, the Dormant Therapies provision (Subtitle L) grants a full fifteen years of monopoly power to any drug applicant whose product meets an "unmet need" and has no

1825 K STREET, NW, SUITE 411, WASHINGTON, DC 20006 | (202) 638-7151 | NCHC.ORG

**Chairman**

Jack Lewin  
*President and CEO,  
Cardiovascular Research Foundation*

**President and CEO**  
John Rother

**Board of Directors**

The Honorable David Durenberger  
*Former U.S. Senator from Minnesota  
Senior Health Policy Fellow,  
University of St. Thomas*

Blair Childs  
*Senior Vice President of Public Affairs,  
Premier, Inc.*

George Diehr  
*Vice President,  
CalPERS Board of Administration*

David Dobbins  
*COO,  
American Legacy Foundation*

Evan Falchuk  
*Vice Chairman,  
Best Doctors, Inc.*

Darryl Leedom  
*National Social Services Secretary,  
The Salvation Army*

Michael Maccoby  
*President,  
The Maccoby Group*

Sonia Millsom  
*Vice President for Payor Strategy,  
Best Doctors, Inc.*

Joe Minarik  
*Senior Vice President and Director of Research,  
Committee for Economic Development*

Ralph Neas  
*President and CEO,  
Generic Pharmaceutical Association*

John Seffrin  
*CEO,  
American Cancer Society*

Damon Silvers  
*Director of Policy and Special Counsel,  
AFL-CIO*

Susan Turney  
*CEO,  
Marshfield Clinic Health System*

Debra Whitman  
*Executive Vice President of Policy, Strategy  
and International Affairs,  
AARP*



competitor with the same moiety. As Columbia University Professor Scott Hemphill, Ph.D. stated before the Subcommittee on Health on June 11, 2014, "It is hard to think of a new chemical entity that would fail this test." Enactment of such a broad and lengthy extension of monopoly power would shatter the incentives for strong generic competition which have helped hold down prescription drug costs in Medicare Part D and the private sector.

Fortunately, granting a long-term monopoly to a brand name manufacturer is not the only option to promote innovation. Other tools, such as increased funding for basic and translational research, public private cooperation, and provision of tax credits or other prizes can help promote the development of dormant therapies without crippling competition. Therefore **NCHC urges the Committee to reject any long-term or broad-based extensions of market exclusivity.**

Ultimately, however, it's not enough to merely avoid worsening the current cost trajectory for prescription drugs. Following years of relatively stable drug expenditures, drug costs are already on the rise, climbing at 10.9% clip in 2014. By 2020, CVS projects that specialty drug costs alone projected to reach \$400 billion. If consumers and taxpayers are to afford the growing cost of prescription drugs over the long term, Congress must take proactive steps to enhance price competition now. **NCHC strongly recommends that any final 21<sup>st</sup> Century Cures legislation include the following pro-competition provisions:**

- **Pass the FAST Generics Act:** This bipartisan legislation, introduced as HR. 5657 by Rep. Steve Stivers (R-OH) and Rep. Peter Welch (D-VT) during the 113<sup>th</sup> Congress would end the misuse of Risk Evaluation and Mitigation Strategies (REMS) to deny drug samples to potential generic competitors- both for biologic and chemical drugs.
- **Assure Adequate Reimbursement for Biosimilars:** The biosimilar pathway established by the Biologics Price Competition and Innovation Act is vital to affordability of biologic medications- for both consumers and taxpayers. But appropriate reimbursement policies are needed to ensure the expected savings from biosimilar competition are realized. In Medicare Part B, for example, Congress should instruct CMS to promptly clarify that biosimilars, like other generic drugs, will be reimbursed under the same Healthcare Common Procedure Coding System (HCPCS) codes as the originator drug.

Just nine months after its launch last June, the 21<sup>st</sup> Century Cures Initiative has helped bring the stakeholder community, lawmakers of both parties, executive branch agencies, and the White House together in a common effort to support innovation. But moving forward with legislation that fails to address affordability would not be reflective of the spirit of cooperation which has characterized the 21<sup>st</sup> Century Cures effort previously. We urge the Committee to remove counterproductive, long-term extensions of monopoly power from this bill and instead take steps to expand competition. When that occurs, NCHC will be eager to advance down the road to 21<sup>st</sup> Century Cures.

Yours truly,

  
John Rother  
President and CEO



Thanks for your request, Heidi. In addition to the 11 specific recommendations in my other memo, I offer the following specific comments in my capacity as a private citizen:

**Section 1181, under Title I, Subtitle J – “Streamlined Data Review”**

I would argue that it is dangerous to set up a system where drug companies can receive new approvals from the FDA based only on “qualified data summaries” that are merely a “summary of clinical data,” with the FDA having discretion to refuse to look at the “full data sets.”

Even under current law, the FDA does not do nearly enough to uncover fraud and misstatements in the full data sets that companies submit.<sup>1</sup> Moreover, there is abundant evidence that trial sponsors regularly misrepresent their full findings when they summarize a clinical trial for purposes of publication.<sup>2</sup> There is no reason to think that their behavior would improve if they knew that they wouldn’t even have to let the FDA see a full data set.

**Section 2081, Standardization of Data in Clinical Trials Registry Data Bank**

This is an admirable start for improving the functionality of ClinicalTrials.gov.

*Enforcement Power Should Be Strengthened*

I would note that the 1-year timeline for implementation may need more teeth – Section 801 of the Food and Drug Administration Amendments Act of 2007<sup>3</sup> requires the Secretary of HHS to start and finish a rulemaking proceeding by 2010 in order to expand ClinicalTrials.gov, yet the NPRM wasn’t issued until late last year (see [http://grants.nih.gov/clinicaltrials\\_fdaaa/](http://grants.nih.gov/clinicaltrials_fdaaa/)), and the final rule is nowhere in sight.

If Congress wants HHS to follow through on its statutory responsibilities before another five years pass, it may need to develop a more stringent enforcement mechanism, such as withholding agency funding. Congress may also wish to undertake an investigation and audit into whether HHS has fulfilled all of the other requirements of 42 U.S.C. § 282(j) about expanding the functionalities of ClinicalTrials.gov.

Moreover, ensuring that “the registry and results data bank is easily used by the public” is arguably putting the cart before the horse. This is because the results data bank is woefully incomplete: a *New England Journal of Medicine* article<sup>4</sup> released on March 12, 2015 looked at over 13,000 clinical trials registered on ClinicalTrials.gov, and alarmingly found that “summary

---

<sup>1</sup> See

[http://www.slate.com/articles/health\\_and\\_science/science/2015/02/fda\\_inspections\\_fraud\\_fabrication\\_and\\_scientific\\_misconduct\\_are\\_hidden\\_from.html?wpsrc=sh\\_all\\_dt\\_tw\\_top](http://www.slate.com/articles/health_and_science/science/2015/02/fda_inspections_fraud_fabrication_and_scientific_misconduct_are_hidden_from.html?wpsrc=sh_all_dt_tw_top) for some recent investigative reporting.

<sup>2</sup> Dwan et al., “Evidence for the Selective Reporting of Analyses and Discrepancies in Clinical Trials: A Systematic Review of Cohort Studies of Clinical Trials,” *PLoS Medicine* (24 June 2014), at <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001666>.

<sup>3</sup> Codified at 42 U.S.C. § 282(j)(3)(D)(i): “To provide more complete results information and to enhance patient access to and understanding of the results of clinical trials, not later than 3 years after September 27, 2007, the Secretary shall by regulation expand the registry and results data bank as provided under this subparagraph.”

<sup>4</sup> See <http://www.nejm.org/doi/full/10.1056/NEJMsa1409364>.

data are not publicly available at ClinicalTrials.gov *for a majority of trials* that are subject to FDAAA provisions.”

When a *majority* of trials are not obeying the law requiring the reporting of results, apparently without any consequence or punishment, it is arguably premature to worry about whether patients can easily navigate ClinicalTrials.gov – *the most important results are not there to find on ClinicalTrials.gov in the first place*. That is, given that trial sponsors are more likely to hide the results of clinical trials that failed than those that succeeded, patients might be grossly misled by the biased subset of results that are currently listed.

#### *Patient Recruitment Should Be Easier*

Next, Section 2081 has a reference to “recruitment information” being integrated into electronic health records. This provision should be spelled out in greater detail and given greater force. **It would be an unbelievably important step forwards if patients could be more easily recruited into clinical trials through matching up eligibility criteria to networks of electronic health records.**

I was recently told by Michael Lauer, director of the Division of Cardiovascular Sciences at the National Heart, Lung, and Blood Institute, that if he funds a \$50 million dollar clinical trial, half of that money, or \$25 million dollars, will be spent on patient recruitment. Patient recruitment into clinical trials is so expensive due to the need to hire so many staff members to travel and find patients by hand, so to speak.

There are some efforts right now to create major networks of electronic health records (such as PCORnet at PCORI, or the NIH Collaboratory, or the HMO Research Network, or the FDA Mini-Sentinel Initiative, or CancerLinQ by the American Society of Clinical Oncology). But the recruitment issue is still unaddressed.

If clinical researchers could register a proposed trial with ClinicalTrials.gov, and then easily export that information (exclusion criteria, etc.) into one or more of the above platforms *so as to recruit patients electronically*, that would be an amazing step forward that would make clinical trials much cheaper and more efficient.

We would then see much more drug development and testing, particularly for drugs and drug uses that do not have a major US market. This will be ever more important in an era of “personalized” medicine -- if a medicine is targeted at 10% or 1% of people with a particular disease, it may be more effective, but it also has a much smaller market than if 100% of people with that disease could be prescribed the drug. We therefore desperately need cheaper ways to test such drugs in rigorous clinical trials that are not as expensive as in the past.

Cheaper clinical trials would also be important for many other reasons. In many instances, substances may be unpatented, and no one has the incentive to pay for a large expensive clinical trial. We would need many more clinical trials on comparative effectiveness for different treatments or about off-label uses. Given how much of medicine has never truly been tested in a rigorous trial, the possibility of cheaper patient recruitment into new clinical trials would be a truly exciting development.

Congress should take note, however, that ethics rules under both HIPAA and the Common Rule (which governs federally funded research under 45 C.F.R. § 46) can set up

needless obstacles to patient recruitment into many clinical trials.<sup>5</sup> Under the relevant HIPAA rule (45 C.F.R. § 164.512(i)(1)(ii)) and the Common Rule, researchers outside of the HIPAA entity cannot contact prospective research subjects unless they *first* go to an IRB and get a waiver of informed consent.<sup>6</sup> But it would be far more straightforward, efficient, and sensible if researchers could quickly and easily check a database (with all the appropriate confidentiality protections, of course) to see who might be eligible for a particular clinical trial, and *then* contact those prospective subjects to see if they would consent to be in the trial.

### **Section 2082, Clinical Trial Data System**

Section 2082 would require the FDA and NIH to enter into a collaborative agreement with an outside entity that would help make de-identified clinical trial data available for further research. This is a tremendously useful step forward in clinical trial transparency, and I applaud it personally. I do have a few suggestions, though:

**First, all clinical trials regulated by the FDA or funded by the NIH should be mandated to participate.** This requirement should come with real teeth, such as revocation of FDA approval or refunds of NIH grants. Otherwise, trial sponsors will ignore the requirements much more than they already ignore the FDAAA requirement to report results (which is simpler than sharing patient-level data).

Second, it might be jumping the gun to assume that the trial data should all be de-identified. The problem with de-identified data is that, by definition, it cannot be matched up with other datasets, because there is no longer enough information to identify which patients are which. Yet matching up with other datasets could be an enormously useful source of new research. Imagine, for example, that a clinical trial dataset is able to be matched up with electronic health records, genomic data, personal records from electronic devices, future Medicare claims, and more. By tying different datasets together, researchers would have *vastly* more opportunities to perform invaluable research that could never take place any other way.

New methods of encryption are being developed that would allow researchers to query and analyze datasets without any of the data ever being decrypted.<sup>7</sup> This would be revolutionary, because individuals' privacy could be fully protected even while allowing invaluable research to carry on. Congress should not forestall such innovative encryption methods by having a blanket requirement that all clinical trial datasets be de-identified. Instead, Congress should craft more nuanced language that allows for the development and use of creative solutions that would respect privacy even while allowing more research to occur.

### **Section 2101, under Subtitle G, Utilizing Real-World Evidence.**

It seems dangerous to me to set up a system in which drug companies can seek approval or satisfy post-approval requirements by using data from "sources other than randomized clinical trials, including from observational studies and registries." Drug companies have a history of

---

<sup>5</sup> See "HIPAA Creating Barriers to Research and Discovery," [http://www.aahcdc.org/policy/reddot/AAHC\\_HIPAA\\_Creating\\_Barriers.pdf](http://www.aahcdc.org/policy/reddot/AAHC_HIPAA_Creating_Barriers.pdf).

<sup>6</sup> See <http://privacyruleandresearch.nih.gov/faq.asp#22>.

<sup>7</sup> See <http://crypto.stanford.edu/craig/easy-fhe.pdf>.

distorting randomized trials in many ways, and the opportunities to distort observational research are vastly greater. The FDA already has discretion to consider such evidence where it is reliable.

### **Section 2201, under Subtitle L: NIH—Federal Data Sharing.**

This section currently says that the NIH “may” require its grant recipients to agree to share their data. This provision is unnecessary as written – the NIH already “may” do so. What is needed is a provision stating that the “NIH *must* require all recipients of grants or other support to share with the public data generated through such research.”<sup>8</sup> It would also be good to add language requiring that data be posted in a *trusted digital repository* with a *persistent digital identifier* (that is, you can’t just post it on your personal website where it could disappear tomorrow; instead, it should be in the digital equivalent of a library where it is catalogued and kept more permanently).

### **Section 5062, under Title V: Modernizing Medical Product Regulation**

Section 5062 proposes that medical devices could be approved based on “well-documented case histories,” and “studies published in peer-reviewed journals.”

This seems a bad idea. Case histories generally cannot show that a device is effective, and are useful for safety purposes only if major problems show up. For example, if a device makes someone drop dead, that is an obvious effect, but if the person doesn’t drop dead, that doesn’t mean the device is safe – perhaps the device increases the risk of long-term damage by 20%, but you can’t know that without doing research that is far more rigorous than “case histories.”

Peer-reviewed articles are also insufficient and untrustworthy for this purpose. For one thing, peer review only looks at the surface validity of the article, but doesn’t review the underlying data. Second, there are many examples of peer-reviewed journal articles that have to be retracted or significantly revised on further investigation. Moreover, peer-reviewed articles are often short and narrowly focused on an academically noteworthy topic, which is not sufficient to warrant FDA approval. Peer reviewed journals simply do not exist to serve the same purpose as FDA review -- that is, to engage in a thorough and often-tedious examination of the entire body of evidence on the efficacy and safety of a device.

---

<sup>8</sup> Barring legal protections such as HIPAA, of course, or the rare cases where data is too voluminous (such as certain astronomy or high-energy physics research).